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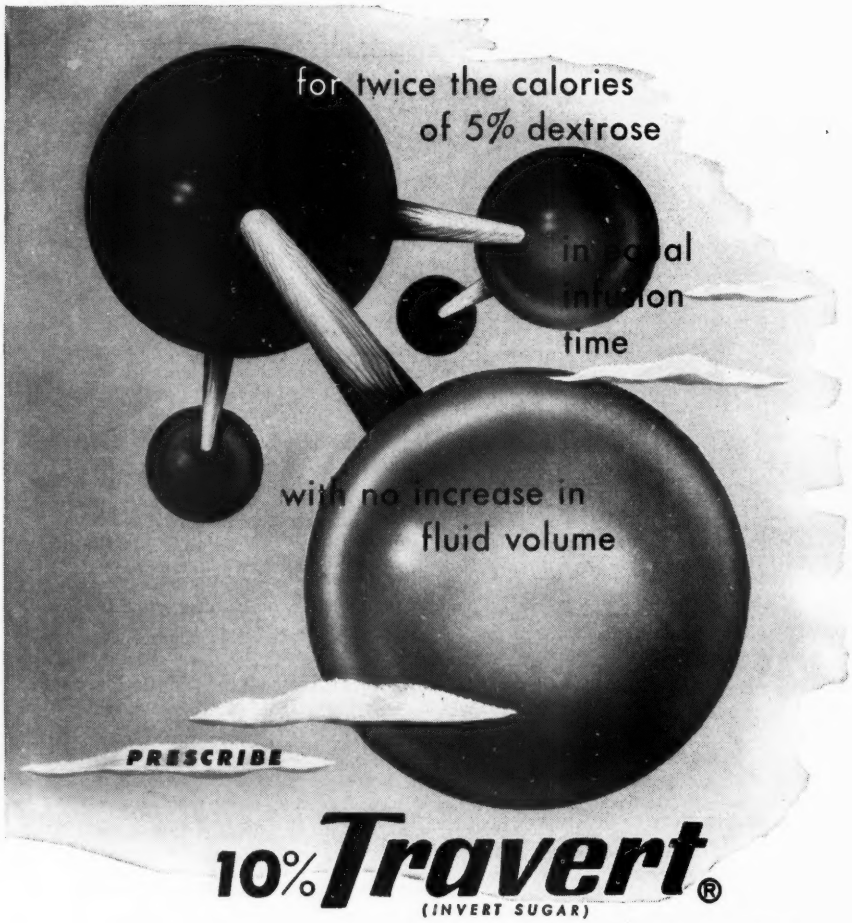

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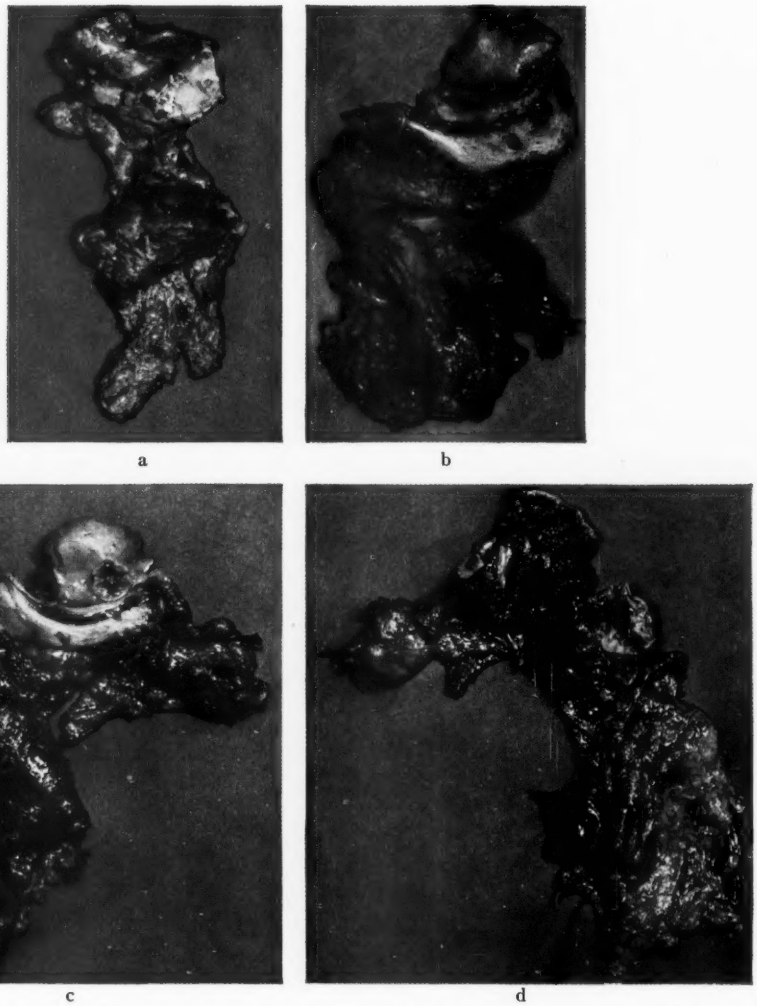

Fig. 1. a, Carcinoma of right lower gingiva treated by combined hemimandibulectomy and right radical neck dissection. b, Persistent carcinoma of tongue following radiation excised in continuity with related perimandibular and jugular lymphatics. c, Carcinoma of floor of mouth treated by en bloc excision. Specimen includes one-half of adjoining tongue and mandible plus related lymphatics. d, Posterior aspect of c. Note contralateral submaxillary dissection and excision in continuity with primary lesion.

Combined Neck and Jaw Resection for Intraoral Carcinoma.—Walter W. Carroll.

SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 94 JANUARY, 1952 NUMBER 1

COMBINED NECK AND JAW RESECTION FOR INTRAORAL CARCINOMA

WALTER W. CARROLL, M.D., F.A.C.S., Chicago, Illinois

A REVIEW of the current literature and an analysis of our own experience impresses one with the present low cure rate for oral cancer other than that arising from the lip. Despite the fact that practically all of these lesions are either visible or palpable or both, such malignant tumors often are not diagnosed in an early phase. In addition, a fair share of such patients often may present serious cardiovascular disease further to complicate the use of definitive surgical treatment. Radiation therapy becomes the treatment of choice for that group. In order to improve upon the present low salvage rates for intraoral cancer the surgeon finds himself working closely with the pathologist and radiotherapist, all co-operating to individualize and outline the treatment best suited to the particular problem at hand. It is apparent that under such variable circumstances somewhat flexible plans of therapy become the rule and in many instances these either are not sufficiently comprehensive or are not actually carried out to completion. While variations in therapy may be mandatory under some circumstances, the similar biologic pattern manifested by many intraoral cancers suggests that a more complete and standardized surgical excision might be applicable to many such patients in our attempts to eradicate the disease. With this thought in mind plus the fact that safe conduct through surgery can now be obtained for the great majority of patients, an evaluation of such a procedure seems appropriate at this time.

From the Department of Surgery, Northwestern University Medical School.

Cancer of the oral cavity comprises about 5 per cent of all human cancer. It is a disease of middle and old age, with males affected about five times as frequently as females. About three-fourths of these lesions are well differentiated, the more anaplastic lesions often being found in the area of the tonsil and base of the tongue. Nine-tenths of these cancers are squamous cell carcinomas. A study of their natural history and biologic aspects reveals that each one produces a few clinical problems peculiar to itself, but their tendency toward predictable cervical node metastases is a common denominator of great practical value. Even though the regional lymph nodes in the neck may become involved by metastases, the disease usually remains within these nodes and tends to be limited to the supraclavicular area for some time before fatal extension takes place.

Since the great majority of oral carcinomas do not invade blood vessels, it is evident that complete control of the disease depends largely upon elimination of the primary lesion with adequate excision of the regional lymph nodes which might contain metastases. Because these tumors metastasize by lymphatic embolization, there has been a tendency for the therapy of the primary to be a separate maneuver with eradication of the related nodes a matter for later consideration if they

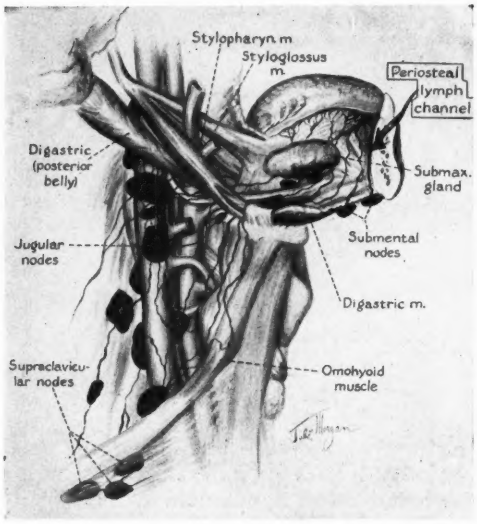

Fig. 2. Relationship of cervical nodes to lymphatic spread of intraoral carcinoma.

show suggestive evidence of metastases. Such a plan of discontinuous therapy has produced some salvage but obviously represents a compromise of the well known concept of a good cancer operation as exemplified by the modern radical mastectomy or the abdominoperineal resection of the rectum. Observations pertaining to the insidious local contiguous extension of these neoplasms and the occasional failure to excise the involved nodes nearest the primary lesion during a delayed dissection suggest that the established concept of dissection and excision of a primary lesion and the nodal metastases in continuity may prove to be applicable to an increasingly large number of orocervical carcinomas.

CLASSIFICATION AND SCOPE

Although the oral cavity produces at least 10 separate clinical varieties, consideration of the various anatomical sites according to the way in which they lend themselves to therapy is practical in the interest of clarity and brevity. It must be evident from the start that such a therapeutic classification presupposes full understanding of the natural biologic history of the cancers so listed. Such a study reveals a high degree of clinicopathological similarity to exist among carcinomas arising from the buccal mucosa near the lower gingival margin, the lower gingiva itself, the floor of the mouth, and the anterolateral two-thirds of the tongue. These constitute approximately 40 per cent of all oral cancer. The essence of this similarity consists in the fact that each produces a substantially high percentage of early lymph node metastases which are so located that both the primary and the secondaries can be excised in continuity. The operation of our choice for this procedure is an en bloc dissection of the involved cervical lymphatics plus a hemimandibulectomy to complete or facilitate the excision of the primary. In order further to clarify this procedure and to locate it within our therapeutic armamentarium I should like to describe these lesions as they have crossed our experience, and to mention some of our problems and disappointments which have led us to conclude that a more vigorous effort must be made in the eradication of oral cancer wherever it lends itself to surgical excision. Our conclusions will be based upon approximately 180 patients with oropharyngeal cancer, in whom 106 lesions were localized to the areas under consideration. Thirty-six of this latter group underwent a complete unilateral neck dissection with or without excision of the primary in continuity.

CARCINOMA OF THE BUCCAL MUCOSA

Carcinomas of the buccal mucosa usually are bulky, papillary, and show a tendency to ulcerate late. There is a verrucous type which has local invasive qualities but less tendency toward lymph node involvement(1). The entire group produces cervical metastases in about 40 per cent of cases (14, 17). They are known for their tendency toward multiple foci of origin, a fact which has given impetus to the more frequent use of radiation as the therapy of choice. Radiation or wide excision may be adequate depending upon the individual lesion. If the lesion is extensive, a full cheek resection with lined pedicle flap replacement must be carried out. When the adjoining surfaces of the lower gingiva become involved, the perimandibular lymphatics are very likely to contain tumor cells and in some

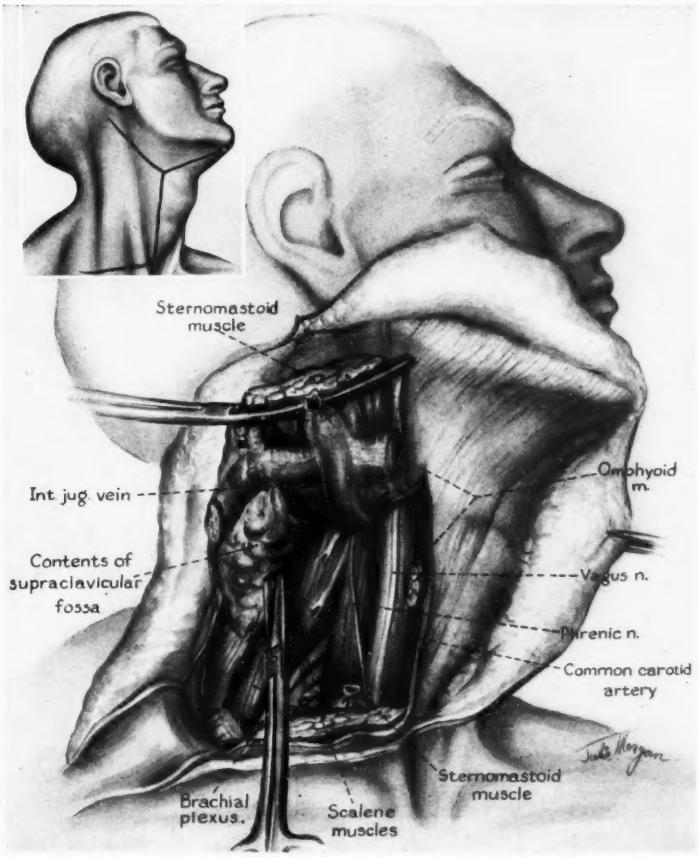

Fig. 3. Combined orocervical resection. After skin flaps are prepared, radical neck dissection is begun from below. Phrenic and vagus nerves are carefully preserved as internal jugular lymphatic mass is mobilized.

the bone may be invaded. The procedure of choice thus becomes a neck dissection with hemimandibulectomy and excision of the cheek lesion in continuity. Immediate plastic repair of the defect should be done through the use of a previously prepared pedicle flap. In the event that a clinical arrest of the primary lesion has been achieved by means of a less vigorous procedure than this, the cervical nodes must be followed carefully and complete homolateral dissection must be carried out in case that they become suspiciously enlarged.

CARCINOMA OF THE LOWER GINGIVA

This cancer formerly was regarded as being relatively benign, showing many of the tendencies of buccal mucosa carcinoma rather than those more malignant characteristics of growths arising from the tongue and floor of the mouth. Closer study and further experience prove this not to be the case. In some series the tendency toward cervical lymph node metastases may be as high as 65 per cent (9, 16, 17). Local contiguous spread is common; the cheek, floor of mouth, and underlying bone may be invaded in 2 out of 3 cases.

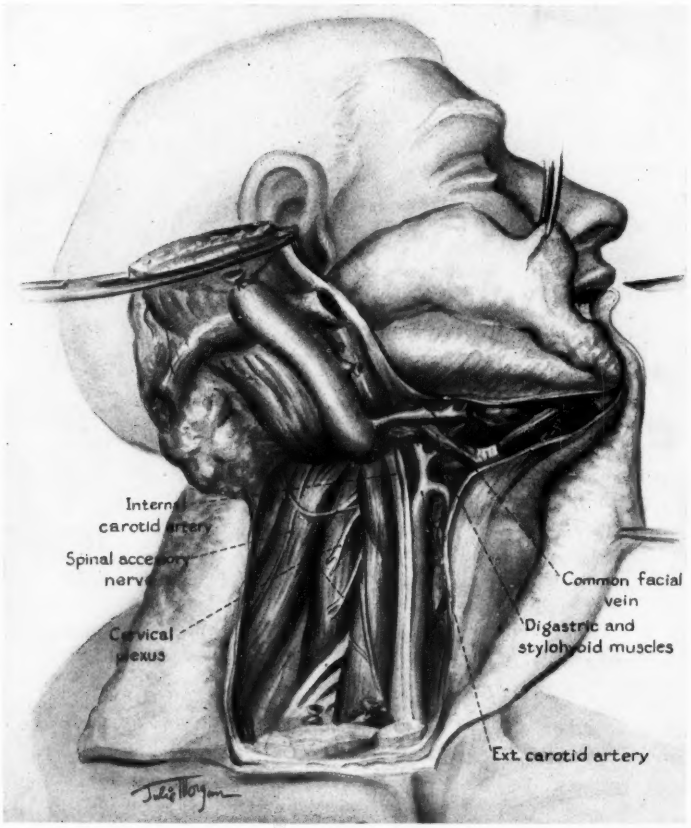

Fig. 4. At level of superior thyroid artery dissection is carried upward to midline and the lip divided. Submaxillary triangle is left intact and included in specimen.

In the past it has been our practice to treat small lesions less than 2 centimeters in diameter with x-ray through an intraoral cone or by means of a radium mold. In the event that lymph nodes were enlarged a period of 3 or 4 months was allowed to elapse in order to determine the effectiveness of treatment of the primary. In the absence of local recurrence homolateral radical neck dissection completed the treatment.

We now realize that the great majority (about 80 per cent) of carcinomas arising from the lower gingiva either will not be controlled by the usual local means or when first seen will manifest some degree of extension into adjoining soft tissue or bone. Osteoradionecrosis from previous treatment may increase the problem. Mattick and Meehan recently reported 101 cases of cancer of the gingiva treated entirely with radiation. No patients with either node or bone involvement were cured. It follows that both the primary lesions and obvious nodal metastases must be excised to obtain better results. Even when the patients present no obvious clinical metastases some 30 per cent of the dissection specimens will yield positive lymph nodes (17).

In actual practice we have found that application of the concept of dissection and excision in continuity of tumor and regional nodes will increase the salvage rate for this treacherous cancer. A radical neck dissection

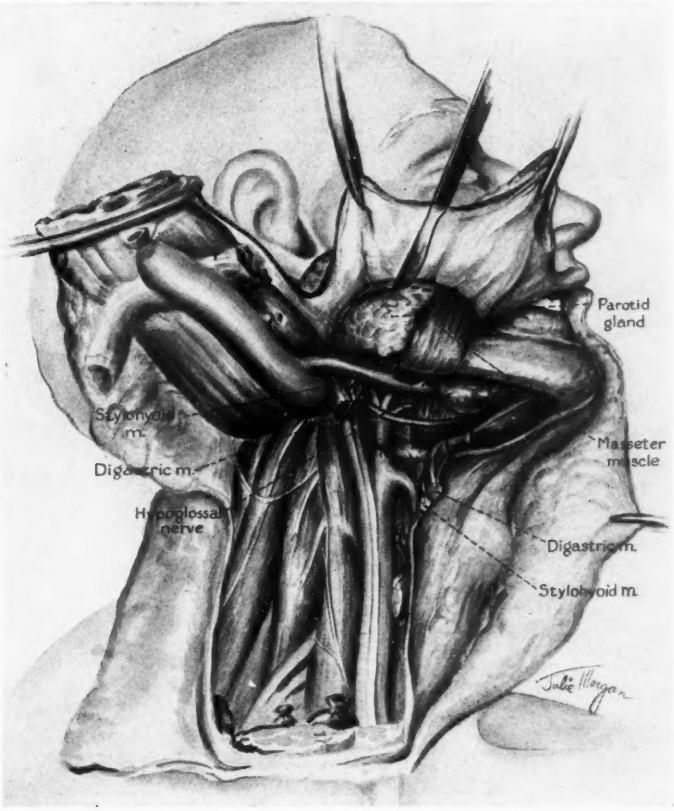

Fig. 5. Buccal gutter is sectioned and cheek elevated with superior skin flap. External carotid artery is ligated. After division of the digastric muscle, high jugular dissection is completed from below. Masseter muscle is divided as high as possible.

combined with hemimandibulectomy has become the operation of choice for such lesions (Figs. 1a and 3 to 6). As much as possible of the masseter and pterygoid muscles should be excised with the mandibular bone to include the related lymphatics draining the gingiva. The wound is closed by apposing the cheek to the cut edge of the tongue and floor of the mouth. A temporary tracheostomy facilitates the postoperative course. Functional and cosmetic results have been quite satisfactory.

CARCINOMA OF ANTERIOR TWO-THIRDS OF TONGUE AND FLOOR OF MOUTH

These lesions lend themselves well to consideration as a single clinical entity not only because of the great similarity in their embryological and anatomical relationships but also because of their similarity in tumor pathogenesis and treatment. Squamous cell carcinomas of these areas metastasize freely to the regional cervical nodes, the incidence being reported in various series as low as 40 per cent and as high as 100 per cent, when first seen by a physician. An incidence of 65 per cent is a good conservative average, with 20 per cent being bilateral (3, 8, 17). While it is well known that the great majority of cervical metastases lateralize into the jugular chain depending upon the location of the primary tumor, it often is forgotten that in about 50 per cent of individuals the lymphatics of the

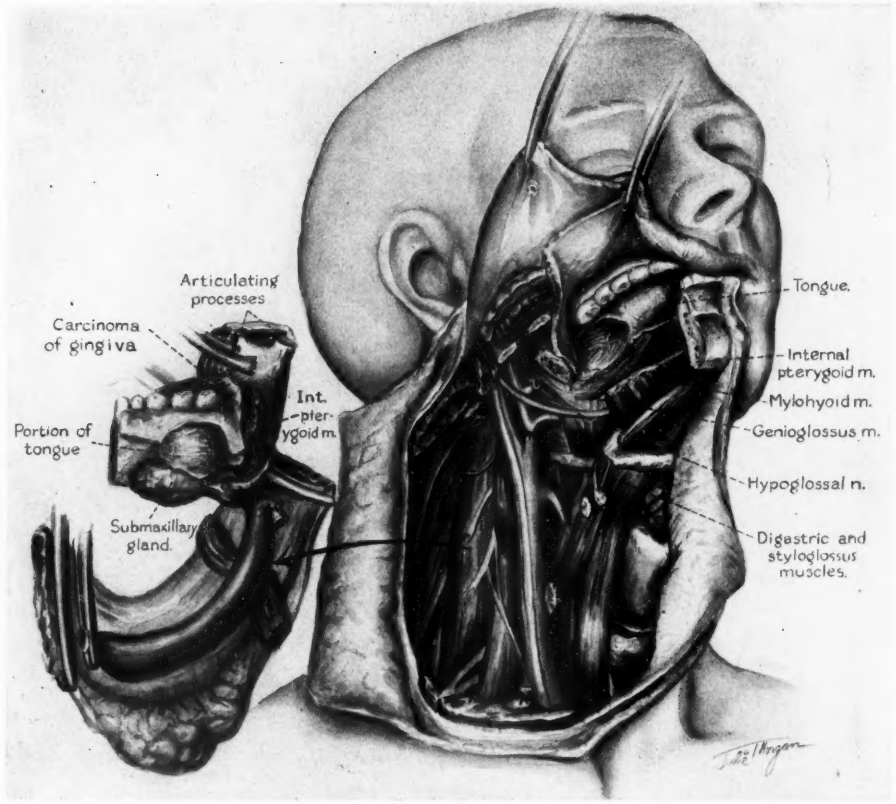

Fig. 6. Following transection of mandibular rami the jaw is rotated lateralward and freed by division of pterygoid muscles. Ligation and division of jugular vein near cranial exit complete excision.

tongue and floor of the mouth pass through the periosteum of the mandible as they drain into the submaxillary lymph nodes (12, 13). This relationship must be remembered in any effort to eradicate these cancers, especially when the lesion lies close to the mandible.

Small cancers of the tip of the tongue, particularly of the papillary type, lend themselves well to simple surgical excision. A therapeutic neck dissection, either unilateral or bilateral, will be necessary in a few of these rare patients, the decision being dependent upon clinical findings during a follow-up period of thorough monthly examinations. Prophylactic neck dissection would not be required in such early lesions, especially if the patient can be seen at regular intervals.

In the past years our treatment of choice in moderately advanced lesions of the tongue and floor of the mouth has been radiotherapy followed by homolateral neck dissection after the primary had been controlled and if the nodes were enlarged. In the presence of apparent control of the primary there has been a growing tendency to perform routine neck dissection in the hope of increasing the total salvage. Such a plan is based on the fact that 39 per cent of patients will yield positive nodes even though not palpable (11). This has been a progressive step, but its benefits have been neutralized by inadequate control of the primary lesion. The ability of radiation, whether external or interstitial or some combination of both, completely to sterilize

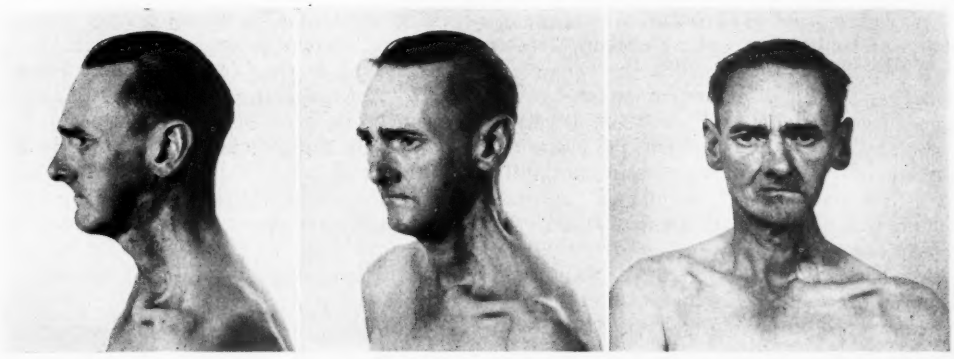

Fig. 7. Left radical neck dissection combined with resection of mandible for carcinoma of posterior lower gingiva after 3 years. Facial contour aided by preserving bone near midline.

the primary lesion is a matter of some question at this time. In view of this observation and with realization of the mechanical efficiency of neck dissection and the more recent possibility of adding hemimandibulectomy to the surgical attack, it might be suggested that further expansion of the therapeutic armamentarium relating to the primary lesion be accomplished. The overall salvage rate in these patients has not exceeded 50 per cent when the lesion is smaller than 2 centimeters in diameter. Counting all patients, the best modern 5 year cure rate for radiation is about 28 per cent (6). It should be recalled that in 1909 Butlin reported 31 per cent survivals from 197 patients treated only by surgery for carcinoma of all parts of the tongue; and his case mortality rate for all procedures was only 10 per cent.

Statistics available in the literature indicate that following the use of various techniques of radiation certain percentages of patients exhibit incomplete regression or persistence of the primary tumor. Thus, Ward and Hendrick found 21 per cent residual tumor in surgically excised previously irradiated carcinomas of the tongue. Various others report 36 per cent, 58 per cent, and 68 per cent of patients in whom the primary was grossly uncontrolled—that is, either had recurred promptly after regression with healing under supposedly adequate treatment, or never had healed at all (4, 15, 5). All of these data bring to our attention the fact that wide surgical excision after irradiation might well eradicate the residual carcinoma in some of these patients and thus be a factor in increasing the incidence of completely controlled primary lesions.

With respect to the regional lymph nodes, the thoroughness of the surgical attack cannot be measured accurately except in those instances in which the primary was completely eliminated. It has not been possible to extract from the various clinical files the records of a sufficiently large number of such patients, but it is fairly well accepted that neck dissection is the method of choice when the nodes are involved. There is some question whether this should be limited to those patients with palpably enlarged nodes (therapeutic dissection) or done in all cases as a routine (so-called prophylactic dissection) once the primary has been controlled. Martin recently has attempted to answer this question and has concluded only in favor of the therapeutic dissection (7). On the basis of our interpretation of his figures, we cannot agree with him. Considering his patients whose primary lesion was controlled and who had no palpable cervical lymph nodes, 48 per cent later developed homolateral positive nodes and an additional 7 per cent developed contralateral positive nodes. In view of the low mortality for such procedures of from 2 to 3 per cent, it seems to us that the risk is not great relative to the large number of patients who would be benefited from a neck dissection.

When the problem of control of the primary lesion and elimination of cervical metastases is resolved in cases in which the tumor approaches the mandibular lymphatics, we are forced to conclude that the most practical method of solving the problem is to excise the primary growth and the nodes in continuity in such a manner as to include all the intervening lymphatics. This of necessity includes a hemimandibulectomy to complete the adequate surgical extirpation. At the present time we are faced with the fact that such an extensive procedure is producing good results in instances of postradiation recurrence or primary extensive involvement. On the other hand, we are withholding this procedure from patients with lesser degrees of malignancy, who undoubtedly would benefit to a greater extent. If this concept is logically pursued we shall find ourselves concluding that the procedure of choice should be a complete homolateral neck dissection, combined with hemimandibulectomy and hemiglossectomy in all instances of moderately advanced carcinomas of this area. If the lesion approaches the midline, a simultaneous contralateral submaxillary dissection in continuity should be added because of the increased risk of cross metastases (Fig. 1 c, d). The finding of positive nodes on the opposite side calls for a complete jugular dissection at a later date, with the vein being preserved when possible.

DISCUSSION

Consideration of these four clinical entities as a unit may at first seem to be an oversimplification of therapeutic planning. Such thinking is based upon the optimistic assumption that these lesions will be seen early enough to allow for some type of local eradication of the primary lesion followed by block neck dissection upon discovery of enlarged regional nodes. There is no denying that an occasional patient may present himself as a logical candidate for such a therapeutic program but by and large this situation seems to be rather rare. Even in these instances control at the primary site many times cannot be achieved through "adequate" treatment. More usual as the clinical picture is that of a local recurrence with contiguous spread into nearby structures, or merely a large primary lesion with extensive local involvement. Thus, tongue and gingival carcinoma may involve the floor of the mouth and vice versa. Osteoradionecrosis from previous treatment often compounds the difficulties. Eventually the relationships become quite intimate so that the regional lymphatics as well as the local anatomical sites present a consolidated problem which can be solved only by en bloc excision along with the adjoining mandible.

SUMMARY

A study of the biologic aspects of carcinomas arising from the buccal mucosa near the lower gingival margin, the lower gingiva itself, the floor of the mouth, and the anterolateral two-thirds of the tongue suggests that they be grouped together when considering treatment of oral cancer. The classification of these lesions into one therapeutic unit is further supported by the fact that they lend themselves well to the application of a fairly new but logical and acceptable type of combined orocervical excision.

A preliminary course of radiation often will be the best method of initiating therapy. In those patients who are candidates for surgery, the definitive extirpation can be carried out after maximum regression or healing has taken place following radiation. The procedure will be a radical neck dissection, hemimandibulectomy, and partial glossectomy all in continuity. At least 2 centimeters of uninvolved soft tissue must be included in this excision when approaching the primary site.

In many of these patients hemimandibulectomy is an essential part of the operation while in others it must be added to diminish the possibilities of local recurrence or to eliminate the persistent pain of previously established osteoradionecrosis. Even though the bone may not grossly be involved by tumor, the removal adds thoroughness to the procedure and greatly facilitates closure of the defect in the floor of the mouth.

In some carefully selected patients preliminary radiation might be eliminated and a direct surgical attack made on the problem. In our hands patients receiving this program of treatment have done remarkably well, but

it is too early to report survival rates. Suffice it to say that a high degree of morbidity has been eliminated. Patients have been rehabilitated quickly and early recurrences have not appeared.

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THE HISTOPATHOLOGY AND CYTOLOGY OF THE CERVIX IN PREGNANCY

ROBERT E. L. NESBITT, JR., M.D., Baltimore, Maryland, and
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FOLLOWING the classic work of Stieve in 1927 only scattered papers have appeared on the cervix during pregnancy. Important among these was the study of Hofbauer on 29 specimens of gravid uteri. He described various signs of epithelial activity, such as reduplication of cell layers, vacuole formation, and some vesicular pleomorphism of nuclei in almost every specimen. While Hofbauer did not believe that these changes were malignant in nature, his thinking was in advance of his time and corresponded to the ideas of current investigators, namely, that these changes might play an important role in the development of later carcinoma.

In 1947, Danforth made an exhaustive review of the fibrous nature of the cervix during pregnancy but paid very little attention to the epithelial changes. McIllrath and Hellestrand in 1947 studied the cervix in pregnancy in order to determine whether certain cervical lesions were caused by, or harbored organisms which could spread into the tissues during labor and the puerperium and thus be responsible for low grade infections so frequently seen in parous women. Vaginal and endocervical smears, as well as cervical biopsies, were taken during the progress of this study. A very comprehensive histologic and cytologic review of the cervical changes in pregnancy was made. In brief, these changes were said to consist of a thickening of the squamous epithelium, decidual formation as early as the tenth week, and glandular changes occurring about the fourth to fifth month. Goblet cells were noted in the glands as well as in the syncytium-like arrangement of epithelial cells. The increase in vascularity, edema, and thinning of the epithelium was also noted. Certain abnormalities of the glandular epithelium were found and were classified as follows: hyperplastic, proliferative, secretory, and mixed types. In 1948, Fluhman studied 89 cervices from pregnant women. Of these, 37 contained cervical polyps and 32 showed erosion. There were 10 instances of carcinoma, 5 of condyloma acuminatum; 3 of endometrial polyps, and 2 of leucoplakia. The outstanding contribution of this study was the conclusion that "erosion" was not a specific pathological entity in pregnancy, but represented adenomatous proliferation of glands, papillary outgrowth, edema and increased vascularity, epidermidization, basal cell hyperactivity, and hypertrophy of the squamous epithelium. Fluhman's paper occasioned considerable discussion, and among the noteworthy comments are those of Novak and Brown. The former felt that inasmuch as the ectocervix was of muellerian derivation it was logical to suppose that, under the estrogenic stimulation of pregnancy, the epithelium of the cervix might respond with basal cell hyperactivity. Brown confirmed the findings of Fluhman, being of the opinion that the proliferation of the glandular structure of the cervix was marked and accounted for the increased bulk of this organ and that the development of so-called erosion was due to the simple procedure of eversion of excess tissue through the external os. In 1950, Murphy and Herbut reviewed the histologic findings in cervical biopsies of 50 pregnant women. Thickening of the superficial squamous layer was found in all cases, while inflammation was present in 64 per cent of the patients. The latter appeared three times as often at the squamocolumnar junction in multiparas than in primiparas. Other quantitative changes included decidual reaction in 22 per cent, epidermidization in 18 per cent, and basal cell hyperactivity in 6 per cent.

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This research was supported by grant from the Damon Runyon Memorial Fund.

Fig. 1. Grade III basal cell hyperactivity of ectocervix.

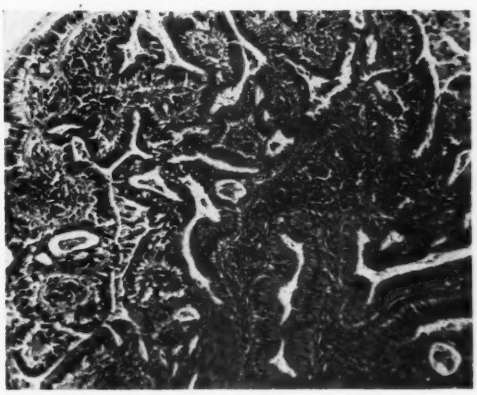

Fig. 2. Gland hyperplasia. Gland epithelial hyperplasia.

In a comprehensive review of the question of carcinoma of the cervix complicating pregnancy, Johnson and Weinfurtner in 1950 commented that the average age was 29 years, or some 14 years less than the average age of occurrence in nonpregnant women. Although they believed that in most instances carcinoma existed prior to the occurrence of pregnancy, they did cite 2 cases of carcinoma in situ. In comment, Novak cautioned against this latter diagnosis in pregnancy, feeling that such changes might be reversible, and cited the work of Epperson. This latter study was conducted upon a large number of women in various stages of pregnancy and the puerperium, in order to delineate clearly the exact morphological changes and their time of occurrence in the cervix of pregnancy. Epperson and co-workers were able to show that under the influence of pregnancy there is an increased activity of epithelium with proliferation both in the stratified squamous layer of the ectocervix and the glandular layer of the endocervix. In the majority of cervices, this type of change is of normal occurrence. In a few, it becomes marked and in 5 instances the changes were so far advanced in the stratified squamous epithelium, that they could not be differentiated by competent observers from the intraepithelial carcinoma. In rather prolonged follow-up, however, these lesions all regressed to normal. Carrow and Greene in a recent paper failed to find these epithelial changes, but this study included only 96 patients.

The investigation which is about to be reported in this paper is a continuation and expansion of the work of Epperson. Its main objective is to correlate the cytological findings from the cervix of pregnancy with the biopsy findings. The present investigators felt that if epithelial activity is a normal finding in a certain percentage of pregnant cervices, then there should be a corresponding deviation from normal in the cervical smears from these individuals. It was further determined to investigate the meaning of these findings and their relationship, if any, to carcinoma in situ.

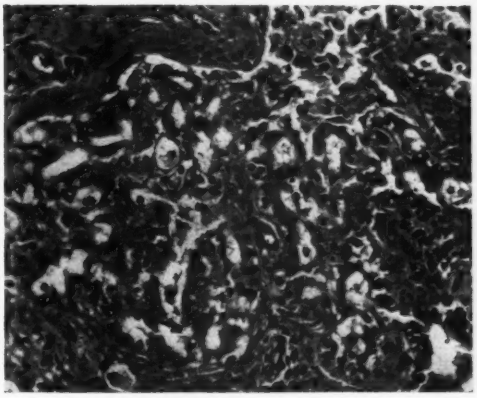

Fig. 3. Adenomatous hyperplasia.

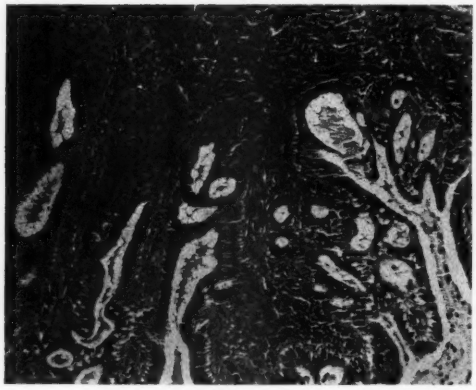

Fig. 4. Epidermidization involving glands alone in endocervix.

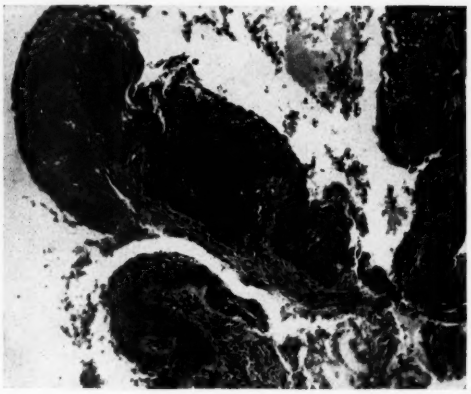

Fig. 5. Basal cell hyperactivity in surface epidermidization.

METHOD

Three hundred pregnant women were selected from the Out-Patient Department of the Johns Hopkins Hospital for study. As nearly as possible, these were consecutive cases and were chosen without reference to gross cervical lesions, although there was no apparent evidence of clinical carcinoma in any of them. The biopsies and smears were taken between the twentieth and thirty-second gestational week, it having been shown in the previous study that the epithelial changes were most marked during this period. A certain number of cases showing marked epithelial activity were restudied later in pregnancy at the time of delivery, and during the postpartum period. Patients who were threatening to abort or who had obstetrical or medical complications, such as toxemia, heart disease, or diabetes, were excluded from the study. Specimens for investigation were taken with the patient in lithotomy position. A clean vaginal speculum was introduced, and the cervix carefully inspected. In cases in which the exudate was marked, the surface was gently swabbed but every effort was made not to disturb the surface cytology. No antiseptic was used prior to biopsy. An Ayre spatula was employed to obtain the cervical smear by the standard technique, whereby the spatula scrapes the surface of the ectocervix with the os used as the center of the arc. A homogeneous, uniform smear was made on a clean glass slide, and the slide fixed in 50 per cent alcohol-ether solution. Biopsies were then taken from each of four quadrants of the cervix at the squamocolumnar junction with a punch biopsy forceps. This forceps was clamped and left in place for several minutes prior to the removal of tissue so as to crush and thrombose the vessels. It was believed that this simple procedure aided in the con-

TABLE I.—DURATION OF PREGNANCY AT TIME OF DELIVERY

	No. cases	Per cent
Premature (1,000–1,499 grams), 28–32 weeks	4	1.33
Premature (1,500–2,499 grams), 32–36 weeks	19	6.33
Term (2,500 grams) 37 weeks	274	91.33
Unknown	3	1.00
Total	300	100.00

TABLE II.—INTERVAL BETWEEN LAST BIOPSY AND DELIVERY

Time, days	No. cases	Per cent
Less than 6	0	—
6– 8	1	0.33
9–14	1	0.33
15–21	4	1.33
22–30	5	1.66
Over 30	286	95.33
Unknown	3	1.00
Total	300	100.00

Fig. 6. Anaplasia in surface epidermidization.

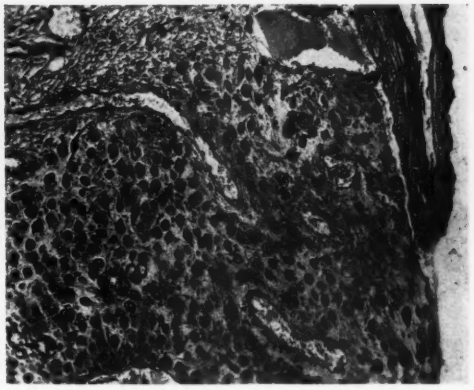

Fig. 7. Decidual reaction of cervix.

servation of blood. Less bleeding was encountered when the clamp was twisted off than when it was removed by direct traction. In the vast majority of cases, bleeding was quite minimal and no special attention was required. Tampax was routinely inserted in the vagina, and the patient was dismissed with instructions to remove it in 6 hours. In a minority of cases, in which bleeding was more profuse, tamponade of the bleeding site with a sponge stick for several minutes was all that was required. A very few patients required silver nitrate cauterization before satisfactory hemostasis was established.

TABLE III.—INFECTION FOLLOWING BIOPSY

Degree of infection	No. cases	Per cent
None	295	98.33
Minimal	0	—
Moderate	1	0.33
Marked	0	—
Unknown	4	1.33

TABLE IV.—TIME OF RUPTURE OF MEMBRANES

	No. cases	Per cent
Prematurely within 1 week of biopsy	2	0.66
Prematurely longer than 1 week of biopsy (several hours before labor)	22 (18)	7.33
During labor, early	65	21.66
During labor, late	206	68.66
Unknown	5	1.66
Total	300	100.00

DISCUSSION

As in the previous study, complications from biopsy during pregnancy were nearly nonexistent, as shown in Tables I through V. There was no undue hemorrhage. In 1 instance, infection in the nature of a nonspecific vaginitis resulted from failure to remove the tampax as directed. There was no increase in the incidence of premature births.

The biopsy specimens were fixed in Zenker's solution and stained with hematoxylin and eosin. The smears after several hours' fixation in the alcohol-ether solution were stained by the standard Papanicolaou technique. The biopsies and smears were examined microscopically, separately, and independently by the two authors. In the event of discrepancy of opinion, the slides were reviewed and a common diagnosis decided upon. At this review session, decisions for repeat biopsies or smears were made. In particular, repeat biopsies were done in the case of those individuals showing

TABLE V.—BLEEDING FOLLOWING BIOPSY

Degree	No. cases	Per cent
Minimal	279	93.0
Moderate	13	4.33
Marked without shock, no treatment	3	1.00
Marked with $AgNO_3$ cauterization	5	1.66
Marked with shock	0	—
Marked with transfusion	0	—
Total	300	100.0

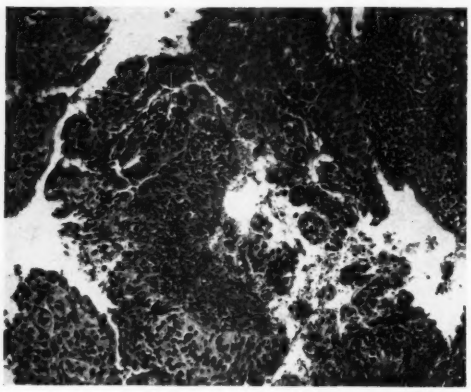

Fig. 8. Intraepithelial carcinoma.

Fig. 9. Normal smear of pregnant cervix.

activity in the epithelium and repeat smears made in both the antepartum and postpartum periods. It is the present intention to follow these individuals for several years. A total of 300 initial biopsies and smears and 41 repeat examinations were carried out. Table VI gives a résumé of the age, race, parity, and gestational period of these patients at the time of biopsy.

As shown in Table VII, 42.3 per cent of the cervices were grossly normal; 30.3 per cent showed simple eversion circumscribing the external os; in 21.3 per cent chronic infection was present as manifest by "erosion," eversion, and a granularity of the surface; while in 5.3 per cent nabothian cysts were visible grossly. In addition, 2 endocervical polyps were found.

There is apparently no uniform classification or terminology describing the changes which take place in the cervix. In this, and in the previous study, an attempt has been made to present such terminology. Thus, basal cell hyperactivity has been used to designate a proliferation of the germinativum or basal layer of the squamous epithelium of the ectocervix. Hyperactivity of this layer has been graded arbitrarily in three degrees depending on the ratio of the thickness of the hyperactive layer to the entire thickness of stratified squamous layer. Accordingly, grade I denotes a hyperactivity of the basal layer so that it constitutes one-fourth of the entire thickness of the epithelium. When this layer makes up one-half of the entire thickness it is designated as grade II, and in cases in which the entire thickness of the ectocervical epithelium is made up of basal cells, the designation grade III is employed. It is important to differentiate grade III basal cell hyperactivity from intraepithelial carcinoma. While this is difficult and requires considerable experience, it should be noted that in the former, the per-

TABLE VI.—ANALYSIS OF 300 CASES STUDIED ACCORDING TO AGE, PARITY, RACE, AND GESTATIONAL PERIOD AT THE TIME OF BIOPSY (INITIAL)

Age, years	No. cases	Per cent	Weeks of gestation			Parity		Race	
			20–24	25–29	30–35	Primigravida	Multipara	Colored	White
Under 15	11	3.66	1	6	4	11	0	11	0
15–24	183	61.00	60	76	47	91	92	173	10
25–34	88	29.33	29	40	19	14	74	82	6
35 and over	18	6.00	4	8	6	2	16	18	0
Total	300	100.00	94	130	76	118	182	284	16

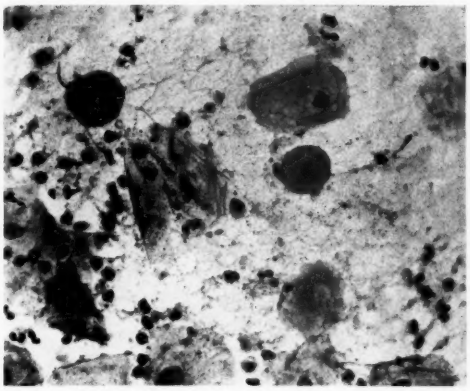

Fig. 10. Postpartum cervical smear.

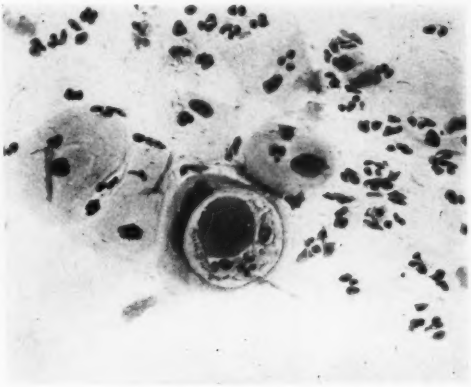

Fig. 11. Histiocytes.

pendicular polarity of cells is maintained. There is considerable uniformity in size and shape of the nuclei and there are few mitotic figures present. Although the nuclei are larger, and often darker staining, because of their basal cell origin, there is no individual hyperchromatism. Many of the basal cell nuclei contain multiple nucleoli and clumps of chromatin (Fig. 1).

Adequate terminology for the changes occurring in the glandular elements of the cervix is arrived at with more difficulty. When there is a simple increase in the total number of mature glands in the endocervix, this condition has been designated as "gland hyperplasia" (Fig. 2). In certain instances in which there is a piling up of the tall columnar cells with basilar located nuclei within the glands themselves, this condition has been termed "glandular epithelial hyperplasia." Care must be taken, however, to make sure that this is a true piling up and not a tangential cut at the base of the gland. When the glandular epithelium undergoes hyperplasia it retains, in many instances, its gland forming potentialities. There thus results the formation of many small, immature glands, and if this process is marked, a true adenomatous pattern may be derived (Fig. 3). Many of the small glands become separated from the mature gland but many retain attachment as demonstrated by serial section. This process has been designated as "adenomatous hyperplasia."

Whether epidermidization occurs by downgrowth of squamous epithelium into the gland or by metaplasia of columnar epithelium to stratified squamous epithelium is not the concern of this paper. It is, however, of the utmost importance to differentiate clearly between gland invasion from carcinoma and epidermidization. In spite of many opinions to the contrary, the authors agree with Meyer who states that transition from epidermidization to carcinoma is unknown. Epidermidization may involve surface epithelium of the endocervix or glands alone, or both in any given biopsy (Figs. 4 and 5). As a matter of fact, the overgrowth of the surface of the endocervix by stratified squamous epithelium is but a natural sequel to the normally occurring eversion of this portion of the cervix in pregnancy. Surface epidermidization becomes a term of diagnostic import in the cervix of pregnancy, for this growth over the everted

TABLE VII.—GROSS FINDINGS IN 300 PREGNANT CERVICES

Lesions	No. cases	Per cent
Normal	127	42.33
Simple eversion and erosion	91	30.33
Chronic infection—nabothian cysts	16	5.33
Chronic infection, erosion, eversion, granular	64	21.33
Polypi	2	0.66
Total	300	100.00

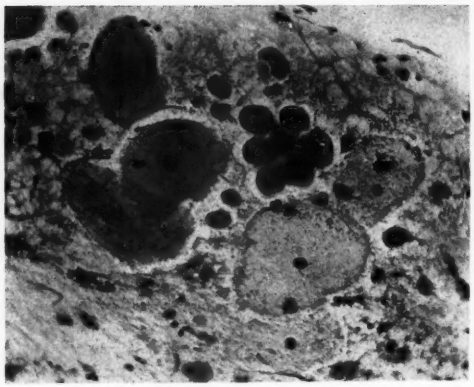

Fig. 12. Superficial and parabasal cells.

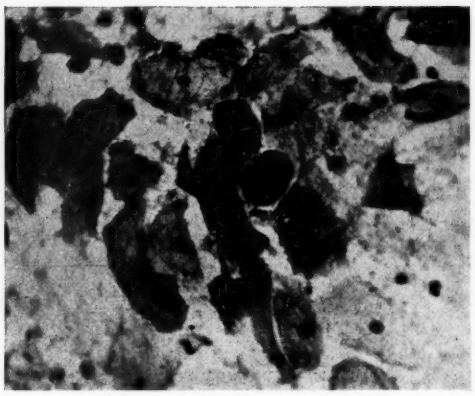

Fig. 13. Atypical parabasal cells.

endocervix takes place rapidly and often comprises only the basal layer. Thus, an impression is given of basal cell hyperactivity or even carcinoma in situ and the differential diagnosis cannot be made unless the significance and etiology of the process is realized. Furthermore, on occasion, surface epidermidization will yield smears containing both normal and abnormal parabasal cells. Figure 6 shows an area of surface epidermidization with actual anaplasia of the squamous cells.

In the present study, nabothian cysts were defined as distended inclusion cysts lined by somewhat flattened glandular epithelium. There were many with dilated glands in the endocervix which were therefore excluded, it being felt that there was insufficient intracystic pressure in the epithelium.

The incidence of decidual reaction varies, of course, with the strictness of the definition employed. There is a very high percentage of so-called "predecidual" change in the cervical stroma, manifested by a swelling of the stromal cells. In this study, we have insisted upon a true decidual change with cells resembling closely those of the endometrium and characterized by large, pale-staining, polygonal cells with wide zones of cytoplasm about a centrally located rather inconspicuous nucleus. Figure 7 exemplifies such a change.

Table VIII gives the incidence, in summary form, of various histological findings in the 300

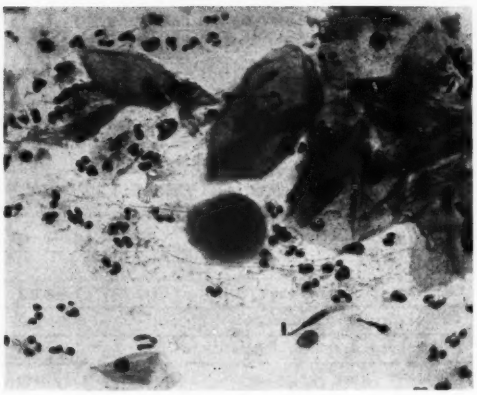

Fig. 14. Atypical navicular cells.

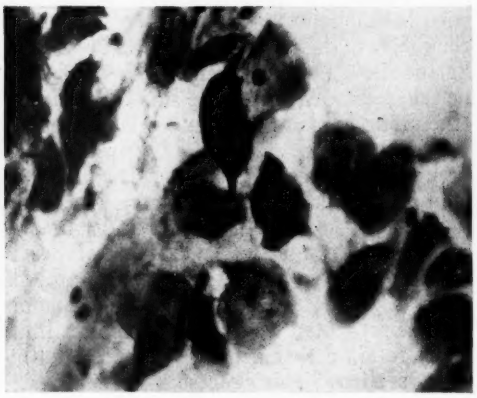

Fig. 15. Atypical parabasal cells.

cervices studied. Of note are the 2 instances of intraepithelial carcinoma and the 3 cases of markedly anaplastic cell change in an extensive area of surface epidermidization.

One of the cases of intraepithelial carcinoma was found during the routine study (Fig. 8), and 1 was referred in but was included in the study group. Both have reverted to normal, the latter being so proved at hysterectomy 6 months postpartum. This brings to a total of 7 the cases of intraepithelial carcinoma followed by the authors (5 in the previous paper). All have reverted to normal and have remained so, 1 longer than 3 years.

A careful survey of the cervical smears from these 300 cervices has shown a general concurrence with the findings of Papanicolaou and Traut. There is a rather characteristic cytology associated with pregnancy (Fig. 9). This change begins to appear during the sixth and seventh week of gestation. Smears taken during early pregnancy resemble those found during the premenstrual phase with a predominance of superficial acidophilic cells with small, pyknotic nuclei. As pregnancy progresses, the acidophilic predominance decreases and basophilic intermediary or navicular cells gain dominance in the smear. The nuclei of these cells are somewhat larger. Generally there is scant mucus and few leucocytes, and the prevailing organism is Bacillus vaginalis. Normally, the deeper cells are rarely seen, and there is only an occasional parabasal cell in evidence and no true basal cells. The general pattern of the navicular cells consists of small, dense clusters.

The cytology of the cervix in pregnancy is altered by many conditions, some of which are poorly understood. As already noted, some degree of inflammation occurs in approximately 88 per cent of the biopsies studied. This factor influences the exfoliated cells of these cervices. Local infection tends to cause a persistence of acidophilic cells, and trichomonas infections are quite prone to cause marked changes in the cells, many appearing truly anaplastic. In addition, there may be a marked leucocytosis, profuse mucus, and myriads of bacteria.

Soon after delivery, there is a shift in cell type and pattern. The navicular type per-

TABLE VIII.—INCIDENCE OF HISTIOLOGIC CHANGES IN THE INITIAL 300 BIOPSIES STUDIED

Lesion	No.	Per cent
Basal cell hyperactivity		
None	271	93.12
Grade I	16	5.49
Grade II	2	0.68
Grade III	2	0.68
Unknown	9	
Gland hyperplasia		
None	199	71.33
Grade I	59	21.14
Grade II	18	6.45
Grade III	3	1.07
Unknown	21	
Gland epithelial hyperplasia		
None	147	52.68
Grade I	89	31.89
Grade II	38	13.62
Grade III	5	1.79
Unknown	21	
Adenomatous hyperplasia		
None	156	55.91
Grade I	82	29.39
Grade II	32	11.46
Grade III	9	3.22
Unknown	21	
Epidermidization		
None	105	37.36
Grade I	47	16.72
Grade II	40	14.23
Grade III	5	1.77
Surface Only	84	29.89
Unknown	19	
Cervicitis		
None	35	11.66
Grade I	120	40.00
Grade II	128	42.66
Grade III	17	5.66
Acute	5	
Subacute	5	
Chronic	290	
Nabothian cyst		
None	121	43.00
Present, single	25	8.89
Present, multiple	135	48.04
Unknown	19	
Decidua		
None	159	54.72
Minimal	83	28.62
Moderate	38	13.10
Marked	10	3.44
Unknown	10	
Basal cell hyperactivity in epidermidization		
None	265	89.22
Grade I	10	3.36
Grade II	19	6.39
Grade III (with anaplasia)	3	1.01
Unknown	3	
Carcinoma		
Intraepithelial	2	0.66
Invasive carcinoma	0	0.0
None	298	99.33
Addenda		
None	258	89.89
No squamous epithelium	8	2.78
No gland epithelium	21	7.31
Other	13	4.33

TABLE IX.—INCIDENCE OF CYTOLOGIC CHANGES IN THE INITIAL 300 CERVICAL SMEARS STUDIED

Cytologic findings	No.	Per cent
Normal parabasal cells		
None	23	7.84
Occasional	205	68.33
Grade I	28	9.55
Grade II	30	10.23
Grade III	7	2.33
Unknown	7	
Atypical parabasal cells		
None	233	79.52
Occasional	38	12.96
Grade I	5	1.70
Grade II	15	5.11
Grade III	2	0.68
Unknown	7	
Atypical navicular cells		
None	180	61.43
Occasional	102	34.81
Grade I	7	2.38
Grade II	4	1.36
Grade III	0	0.0
Unknown	7	
Atypical superficial cells		
None	251	85.66
Occasional	13	4.43
Grade I	19	6.48
Grade II	7	2.38
Grade III	3	1.02
Unknown	7	
Predominant cell type		
Superficial cells	6	2.04
Navicular cells	287	97.95
Parabasal cells	0	0.0
Basal cells	0	0.0
Inflammatory cells		
None	24	8.13
Occasional	25	8.47
Grade I	105	35.59
Grade II	114	38.64
Grade III	27	9.15
Unknown	5	
Histiocytes		
Grade I	33	11.18
Grade II	11	3.72
Grade III	2	0.67
Bacteria		
None	36	12.32
Minimal	97	33.21
Moderate	125	42.80
Marked	34	11.64
Unknown	8	
Addenda		
None	244	81.60
No smear	9	3.01
Poor stain	11	3.67
Poor differentiation	23	7.69
No diagnosis possible	12	4.01
Unknown	1	

TABLE X.—CORRELATION OF FREQUENCY OF BASAL CELL HYPERACTIVITY (BIOPSY) WITH FREQUENCY OF PARABASAL CELLS (SMEAR)

		Basal cell hyperactivity			
		Present 20		Absent 271	
		No.	Per cent	No.	Per cent
Parabasal cells	Normal	6	30.0	59	21.8
	Atypical	11	55.0	47	17.3
Total		17	85.0	106	39.1

*Occasional normal parabasal cells omitted
Chi square = 16.1

sists during the first week postpartum, but toward the end of this time, the cells appear singly or in groups, and are quite atypical with vacuolated cytoplasm and small, even pyknotic nuclei. For several days there is a progressive increase in the entire basal cells. These become quite numerous and may seem to be transition cells, as if there were progressive alterations to produce cells of the more superficial type. Parabasal cells in general have large nuclei and large paranuclear vacuoles are present in these cells postpartum (Fig. 10). They tend to form dense clumps and within these clusters of cells variation in size and shape of nuclei is apparent. Some of the nuclei are markedly enlarged and deep staining even in normal cases. This is in contrast to the antepartum smear which shows no similar changes under normal circumstances. Histiocytes, too, are quite numerous in the postpartum state and some are very large and markedly phagocytic (Fig. 11). As would be expected there are numerous plasma cells and polymorphonuclear leucocytes. As the days pass the typical vacuolated parabasal cells disappear and by the tenth to the fourteenth day postpartum the acidophilic predominance of superficial cells has again monopolized the smear.

In evaluating the antepartum smears no regard was paid to the general classification of Papanicolaou but each cell type was evaluated individually so as to give its incidence during pregnancy. An arbitrary grading of cell types was undertaken and the relative incidence of each type determined. If a particular type cell was seen only once in several high

TABLE XI.—CORRELATION OF FREQUENCY OF EPIDERMIDIZATION (BIOPSY) WITH FREQUENCY OF PARABASAL CELLS (SMEAR)

		Present 176		Absent 105	
		No. cases	Per cent	No. cases	Per cent
Parabasal cells	Normal	41	23.3	23	21.9
	Atypical	37	21.0	23	21.9

Occasional normal parabasal cells omitted

power fields the designation "occasional" was employed. Grade I required that the cells be present in every high power field examination, but that all cells appear singly. When the cells were present in every high power field, and there were occasional clumps shown, the grade was designated as II. Grade III showed clumps of cells in each high power field examined under the microscope. In Table XII, a tabulation of the number and percentage of each cell type in the 300 smears is shown. It should be noted that the superficial navicular and parabasal cells have been further analyzed by dividing each into normal and atypical groups. By "normal" is meant that the cell type conforms to the general configuration and characteristics of its particular layer of epithelium. On the other hand, by "atypical" the cells must have lost the configuration and characteristics ascribed to their particular layer, and have undergone nuclear or cytoplasmic alterations. In this group, the nuclei may be dark staining, greatly enlarged or actively dividing (Figs. 13, 14, 15). Some of these cells are distorted to the point that it is impossible to determine the layer from which they originated. However, since the basal layers are usually more undifferentiated and primitive, most of the latter group have been included under atypical "parabasal cells." In no instance were there typical cytologic changes diagnostic of malignant disease, although in approximately 0.7 per cent of the initial smears there was suspicion of this diagnosis. In 65 of the 300 initial smears at least grade I normal basal cells, or 21.6 per cent, were present.

Table X is of marked significance. Despite the fact that only 20 cases of 300 biopsies showed basal cell hyperactivity, there is a distinct correlation between the occurrence of

TABLE XII.—FOLLOW-UP BIOPSY OF 41 CERVICES, ABNORMAL AT INITIAL BIOPSY

	Antepartum		Postpartum		
	I No.	II No.	6 wks. or less No.	7–12wks. No.	13wks. No.
Basal cell hyperactivity	6	2	0	1	0
Gland changes	38	11	4	1	5
Epidermidization	28	6	3	1	2
Cervicitis	38	11	4	1	5
Normal parabasal cells	39	8	8	3	3
Atypical parabasal cells	25	5	6	1	3

basal cell hyperactivity in the biopsy and the appearance of parabasal cells in the smear. If normal and abnormal parabasal cells are grouped, they appeared in 85 per cent of those cases showing basal cell hyperactivity by biopsy, while they appeared in only 39 per cent of those in which basal cell hyperactivity was absent. The probability of this finding occurring by chance, even though the number of cases in which the basal cell activity was present was small, is less than 1 in 3,000,000. No such correlation exists between the occurrence of epidermidization on biopsy and the finding of parabasal cells on smear (Table XI).

Table XII shows a tendency for those changes signifying abnormal epithelial activity, such as basal cell hyperactivity, epidermidization, normal and atypical parabasal cells, to regress as term approaches and to disappear almost entirely between the seventh and twelfth week postpartum. A patient showing a dyscaryotic prenatal smear is apt to retain this longer in the puerperium than she does an abnormal biopsy. This whole process of recession may be a reflection of estrogen withdrawal.

CONCLUSIONS

Cervical biopsies and smears were studied from 300 pregnant patients, without untoward clinical effects.

The changes noted at biopsy were as follows: (1) basal cell hyperactivity in 6.8 per cent; (2) gland hyperplasia in 28.7 per cent; (3) gland epithelial hyperplasia in 47.4 per cent; (4) adenomatous hyperplasia in 44.1 per cent; (5) epidermidization in 62.7 per cent; (6)

basal hyperactivity in epidermidization in 10.7 per cent; (7) intraepithelial carcinoma in 0.66 per cent; Upon study of the smears, normal parabasal cells were seen in 92.2 per cent (22.11 per cent grade 1 or more) and abnormal parabasal cells in 20.5 per cent.

There is a marked correlation between the occurrence of parabasal cells and basal cell hyperactivity. These changes regress within 7 to 12 weeks postpartum in the histologic sections, but the smears tend to remain abnormal for a longer period. The latter point suggests the importance of the smear as a tool in the follow-up of suspicious cases.

It would seem that caution should be exercised in the final assessment and treatment of cases during pregnancy that fulfill the usual histologic criteria for intraepithelial carcinoma of the cervix.

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THE BLOOD VOLUME IN PRE-ECLAMPSIA AS DETERMINED WITH P^{32} LABELED RED BLOOD CELLS

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USING the vital red dye and T-1824 dye methods for the determination of blood volume, Dieckmann, and Freis and Kenny found that in patients with pre-eclampsia and eclampsia there was a significant reduction in the plasma volume. In neither paper was the total red cell volume in these disease states discussed. Since such patients are frequently considered to be anemic, it was considered of interest to determine the total red cell volume as well as the plasma volume in these patients.

METHODS

The blood volume was determined in 8 women with pre-eclampsia with P^{32} labeled red blood cells by a modification (2) of the method of Hevesy and Zerahn. These women were all in the last trimester of pregnancy and were clinically diagnosed as having pre-eclampsia from the history of edema, headaches, visual disturbances or epigastric pain, and the finding of a blood pressure above 140/90 and an albuminuria. Edema, hypertension, and albuminuria were present in all 8 patients, and in addition one or more of the other signs and symptoms mentioned were present. The data are presented in Table I.

DISCUSSION

In a series of 47 women, the average blood volume in the third trimester of pregnancy has been found to be 72.8 cubic centimeters per kilogram body weight; the total red cell volume 24.7 cubic centimeters per kilogram; and the plasma volume 47.5 cubic centimeters per kilogram. The average hematocrit was 34.0 (1). These 8 pre-eclamptic women show on an average a reduction in their blood volume of 18.9 cubic centimeters per kilogram (26 per cent), in the total red cell volume of 4 cubic centimeters per kilogram (16 per cent) and in the plasma volume a reduction of 14.7 cubic centimeters per kilogram (31 per cent).

The difference (18.9 c.c./kgm.—(14.7+4.0 c.c./kgm.) =0.2 c.c.) between the sum of the decreased total red cell volume and the plasma volume is due to the volume occupied by the white blood cells. Therefore, in the pre-eclamptic state the general finding is that of anemia and a low plasma volume. The higher hematocrit merely reflects a greater decrease in the plasma volume than in the total red cell volume and gives a false picture of the total oxygen carrying capacity of the blood.

The relationship between these findings of a reduction in total red cell volume and plasma volume and the etiology and symptomatology of this disease is not understood.

CONCLUSIONS

1. The blood volume has been determined in 8 patients with pre-eclampsia.

2. There is an average reduction of 26 per cent in the blood volume, 16 per cent in the total red cell volume, and 31 per cent in the plasma volume.

TABLE I.—RESULTS OF STUDY

Patient	Blood volume*	Total red cell volume*	Plasma volume*	Hematocrit
C. W.	57.1	27.4	29.4	46.0
F. C.	50.3	17.1	33.2	34.0
L. M.	48.6	19.9	28.3	40.0
ADLR	55.4	22.1	32.6	40.0
L. B.	56.0	17.4	38.6	31.0
F. S.	42.5	17.4	24.7	41.0
M. G.	54.9	19.8	34.6	36.0
W. M.	66.6	24.7	41.3	37.0
Average	53.9	20.7	32.8	38.1

*In c.c./kgm. body weight.

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This study was supported in part by the Atomic Energy Commission.

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THE EFFECT OF STIMULATION OF THE LOWER INTRATHORACIC PORTION OF THE VAGUS NERVE ON THE CARDIOVASCULAR SYSTEM OF DOGS

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A FEW reports of death during or immediately after vagotomy performed for peptic ulcer have appeared in the literature. Moore and his associates reported a case in which transthoracic vagotomy was performed because of repeated severe gastric hemorrhages. No evidence of peptic ulcer was found. The patient died about 48 hours after operation from difficulties that appeared to be associated with the anesthetic but could have resulted from vasovagal reflexes causing cardiac arrest. A second report by Weeks, Ryan, and Van Hoy concerns a patient with chronic duodenal ulcer, who was undergoing a transthoracic vagotomy. During the manipulation of the right vagus nerve, bradycardia developed. After a short period bradycardia ceased, the operation was continued, and the right vagus nerve was divided. Almost immediately bradycardia again developed, the anesthetist began having difficulty with the patient's respiration, and cardiac standstill occurred. Under treatment the heart action started and returned to normal rhythm for a short time, but finally stopped and failed to respond.

These deaths reported during and after vagotomy may have been due to anesthesia. However, the possibility that they were due to vagal reflexes set up during stimulation or sectioning of the vagi cannot be ignored. With this possibility in mind, experiments were done to study the effect of stimulation of the lower intrathoracic portion of the vagus nerves on the cardiovascular system.

These experiments deal entirely with the lower intrathoracic portion of the vagi between the hilus of the lung and the diaphragm; it is at this level that vagotomy for peptic ulcer is performed. The results of this work should not be confused with the effect of vagal stimulation in the cervical region as described in textbooks of physiology. The textbooks (1, 2) usually state that electrical stimulation of the cervical portion of the vagi causes a decrease in pulse rate and blood pressure. Needless to say, stimulation of the lower thoracic vagi may not necessarily produce the same effect as stimulation of the cervical vagi.

The experiments were designed to determine: (a) the effect on the cardiovascular system of various types of stimuli applied to the lower intrathoracic portion of the vagi, (b) the efficacy of certain drugs in preventing or inhibiting the cardiovascular responses, and (c) the anatomical and physiological basis for the results of intrathoracic vagal stimulation. The stimuli tested were those that might be expected to occur in patients undergoing vagotomy. Four types of stimuli were employed: (1) traction (Fig. 3), (2) electrical stimulation by means of a current obtained with an induction coil, (3) cutting, and (4) crushing by clamping with a hemostat (Fig. 4).

METHOD

A group of 15 healthy mongrel dogs weighing between 10 and 28 kilograms were used. All received endotracheal anesthesia with controlled respirations. Induction was accomplished with ether, chloroform, or cyclopropane, and anesthesia was maintained with ether or cyclopropane. Four of the animals were given curare in addition to general anesthesia. Thus, the experiments were performed under conditions of anesthesia simulating closely those used in the human.

From the Experimental Surgery Laboratory, University of California School of Medicine, San Francisco. This work was aided by a grant from the Charles D. Kaeding Fund.

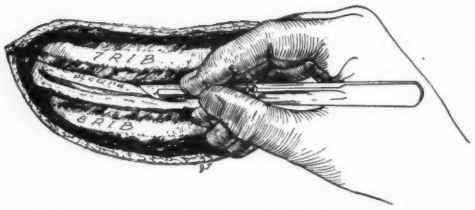

Fig. 1. The animal is placed in the right lateral position and the pleural cavity entered through an incision in the seventh interspace.

The anesthetized animals were placed in the right lateral position, and with aseptic surgical technique the lower intrathoracic vagi were exposed through an incision in the left seventh intercostal space (Fig. 1). The esophagus with the attached vagi was mobilized. The right and left vagi, along with any communicating branches, were dissected and isolated from the esophagus from the level of the diaphragm to the level of the hilus of the lung (Fig. 2).

During application of the various stimuli, the blood pressure and pulse were recorded on a kymograph connected with a cannula in the right femoral artery. The cardiac effects during vagal stimulation were recorded with an electrocardiograph.

RESULTS

Effects of stimulation. Traction on one or both vagi was carried out in 14 dogs and in all dogs produced a definite alteration in blood pressure which usually was a rise but occasionally was a fall. The response varied from 2 to 37 millimeters of mercury. A consistently greater response to stimulation was not obtained by traction on either the right or the left vagus, nor by traction on both vagi. The blood pressure alterations varied from dog to dog but were constant for each individual animal (Fig. 5).

Electrical stimulation of the vagi was carried out in 8 dogs and always caused a blood pressure response. This was usually an increase, but occasionally there was a fall in blood pressure. Again the degree of response varied considerably (from 2 to 37 mm. Hg). As with traction, neither the right nor left vagus, nor both, consistently gave the greatest response to stimulation. The degree of alteration varied from dog to dog but was constant for each animal (Fig. 5).

Division and crushing of the vagi were carried out in 5 dogs. A blood pressure response usually occurred, but it was variable and was always less than that obtained by traction or electrical stimulation. In 2 animals the cervical vagi were sectioned, and in 1 the cervical vagi were blocked with procaine. None of these animals showed any immediate or delayed alteration in blood pressure or pulse rate on division or crushing of the thoracic vagi.

The changes in pulse rate caused by these 4 stimuli were variable, inconstant, of small amplitude and without definite relationship to the blood pressure alterations.

Electrocardiographic tracings were made in 5 animals. Only 2 animals showed any changes whatsoever and these were minor in nature (Fig. 5). No arrhythmia or evidence of myocardial damage was observed.

The only constant response of the cardiovascular system to stimulation of the lower intrathoracic vagi was a transient alteration of blood pressure following traction or electrical stimulation.

Effect of drugs on response to stimulation. Four drugs were tested for their value in inhibiting the cardiovascular responses to traction and electrical stimulation: atropine, dibenamine, procaine, and tetraethylammonium bromide.

Atropine, a commonly used parasympathetic blocking agent, was given to 7 animals. Three milligrams were given intravenously. This is two to three times the calculated dose necessary to paralyze the vagus. After 10 minutes the stimuli were applied. The drug was completely ineffective in either abolishing or inhibiting the blood pressure responses to traction or electrical stimulation (Fig. 6). The only instance in which atropine was effective was in 1 animal in which the cervical vagi were sectioned and the distal end then stimulated electrically. Normally a marked decrease in blood pressure and pulse rate occurs; atropine abolished this response.

Dibenamine was administered to 3 dogs in a dose of 20 milligrams per kilogram of body weight. Traction and electrical stimulation

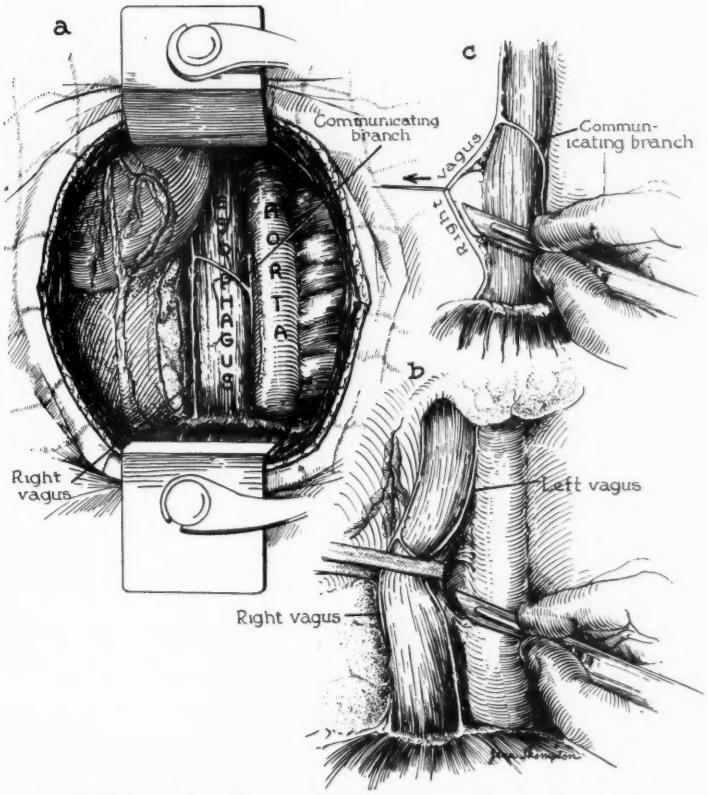

Fig. 2. The pleura is incised over the esophagus which is mobilized with the attached vagi. The right and left vagi, along with any communicating branches, are then dissected from the esophagus from the hilus of the lung to the diaphragm.

were applied to the lower intrathoracic vagi 30 minutes after the injection. In each instance this drug completely blocked the blood pressure and pulse responses to both traction and electrical stimulation (Fig. 7).

An injection of 6 cubic centimeters of a 1 per cent solution of procaine (without adrenalin) was made in and around each vagus nerve in 4 dogs. After 20 to 30 minutes the stimuli were applied. In 2 animals the procaine was injected both proximal and distal to the point of stimulation, in 1 animal it was injected proximally only and in the fourth dog it was injected into the cervical vagi and the thoracic vagi were stimulated in the usual manner. In each of the 4 animals procaine completely abolished the effect of electrical stimulation (Fig. 7), but was without effect upon the response to traction even when traction was exerted upon the thoracic vagi after procainizing the cervical vagi. The fact that the effect of electrical stimulation could be abolished by proximal blocking of the vagi indicates only that the vasomotor reflex involved passes along afferent fibers to the central nervous system and not along the efferent vagal fibers.

Thus, atropine, a parasympathetic blocking agent, was without effect whereas dibenamine, a sympathetic blocking agent, completely abolished the blood pressure response to stimulation of the thoracic vagi. Both agents

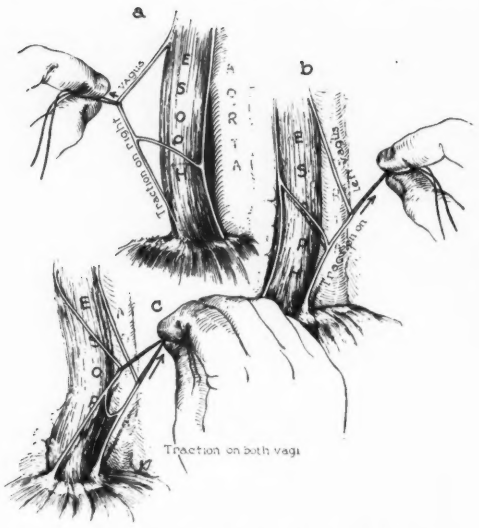

Fig. 3. Illustrating the method of applying traction on the right, left, and on both vagi.

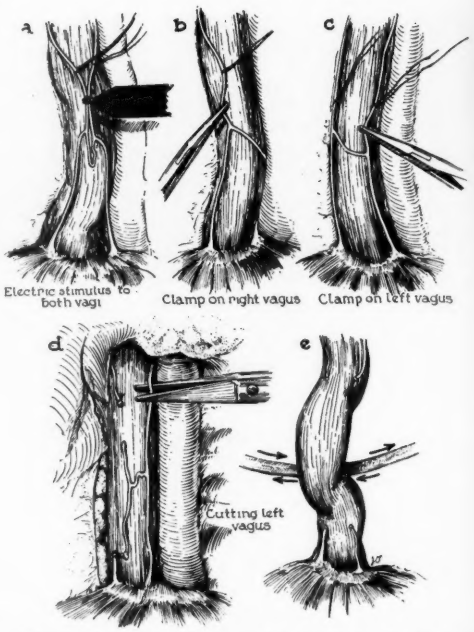

Fig. 4. The other methods used in vagal stimulation were (a) electrical, (b and c) crushing, and (d) cutting. In (e) the esophagus is rotated to be sure that all vagal fibers have been divided.

blocked the usual slight alterations in the pulse rate.

Anatomical and physiological studies. In an attempt to place these experimental results upon a clearcut anatomical and physiological basis, traction and electrical stimulation were applied to the cervical vagi as well as the thoracic vagi and the effects compared both before and after administration of procaine, dibenamine, and atropine. Finally, the effects of traction and electrical stimulation of the thoracic vagi after sectioning the cervical vagi were noted. These experiments were performed on 3 dogs.

Traction on the thoracic and on the cervical vagi gave identical responses. Electrical stimulation of the thoracic vagi usually caused an increase in blood pressure. Electrical stimulation of the cervical vagi, on the other hand, always caused a marked decrease in blood pressure (Fig. 8). Procainization of the cervical vagi failed to abolish the blood pressure response to traction on the thoracic vagi, but either abolished or greatly decreased the response to electrical stimulation (Fig. 9). Procaine, atropine, and dibenamine had an identical effect on the responses obtained with the cervical vagi as with the thoracic vagi.

Reflex arc. The results of these experiments indicate that traction and electrical stimulation of the lower intrathoracic vagi cause a definite and constant alteration in blood pressure with little or no change in the pulse rate or the electrocardiogram. This would seem to indicate that vagal stimulation affects primarily the vasomotor centers of the central nervous system. The reflex arc involved during stimulation of the lower intrathoracic vagi can be worked out from the experimental findings.

The afferent limb of this arc runs up the vagus nerve to the vasomotor centers in the central nervous system (Fig. 10). The experimental evidence for this statement is as follows: (1) Traction of the thoracic and of the cervical vagi gives an identical response. (2) After sectioning of the cervical vagi, traction

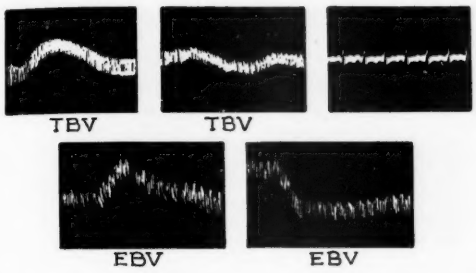

Fig. 5. Kymographic tracings showing the variable effect of mechanical (TBV) and electrical (EBV) stimulation of the intrathoracic vagi upon the blood pressure. The electrocardiographic tracing was taken during mechanical stimulation of the vagi and shows that there was no consistent cardiac effect.

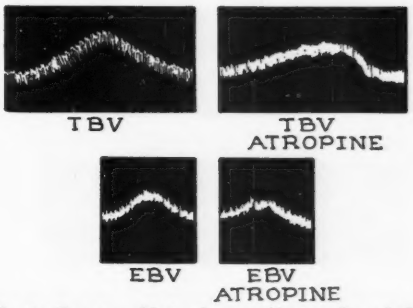

Fig. 6. Kymographic tracings 10 minutes after administration of 3 milligrams of atropine intravenously. Atropine was without effect in inhibiting or abolishing the blood pressure response to mechanical (TBV) or electrical (EBV) stimulation of the intrathoracic vagi.

upon the thoracic vagi causes no blood pressure alteration, nor does traction upon a distal cervical vagus. However, traction on the proximal cervical vagi gives the typical blood pressure response for that animal. (3) Electrical stimulation of the cervical vagi gives a marked decrease in both pulse rate and blood pressure. When the cervical vagi are sectioned, stimulation of the proximal end gives the typical blood pressure response for the animal, while electrical stimulation of the distal portion gives a marked decrease in pulse rate and blood pressure due to the stimulation of the parasympathetic nerves to the heart. (4) The response to electrical stimulation of the thoracic vagi is abolished or greatly decreased by severing the cervical vagi. This indicates that all or the majority of fibers responding to electrical stimulation run in the vagus but a portion may run in the viscerosensory or afferent sympathetic nerves. (5) Procaine injected just proximal to the point of electrical stimulation of the thoracic vagi completely abolishes the blood pressure response. Thus, it is evident that the fibers stimulated by traction and by electrical impulse applied to the lower intrathoracic vagi run in an afferent direction to the central nervous system.

The efferent limb of this reflex arc runs in the sympathetic portion of the autonomic nervous system. The experimental evidence for this conclusion is as follows: (1) Atropine is without effect in abolishing or inhibiting the blood pressure response, yet it will abolish all responses to stimulation of the efferent vagal fibers as noted after electrical stimulation of the distal cervical vagi. (2) Dibenamine, a specific sympathetic blocking agent, abolishes all blood pressure and pulse responses to both traction and electrical stimulation. The fact that atropine is without effect does not mediate against the vagus carrying afferent fibers to the central nervous system, for atropine is peripheral in its action and does not affect the central nervous system synapses.

Thus, the essential reflex arc involved during stimulation of the lower intrathoracic vagi consists of an afferent limb running up the vagus and an efferent limb running in the sympathetic portion of the autonomic system.

Effect of curare. The anesthetic agents used, as indicated, were those which might apply to the human patient undergoing vagotomy. Because at the University Hospital many transthoracic operations are done under curare-nitrous oxide anesthesia, it appeared desirable to determine what effect curare has on the autonomic nervous system. Ether was used in these experiments since no significant difference in experimental results was noted whether cyclopropane or ether was used, and the use of ether was technically simpler.

A dog weighing 9.3 kilograms was anesthetized and the cervical vagus was stimulated electrically with the usual cardiac effect of lowered blood pressure and slowed pulse rate. Intocostrin was injected intravenously in a dose of 80 units, which is comparable to twice the maximum dose used clinically. On electrical stimulation of the peripheral portion of

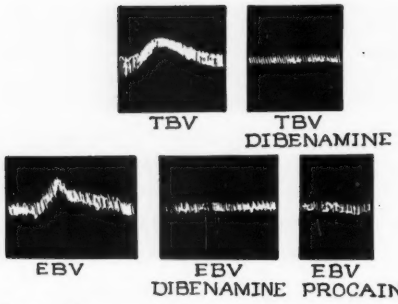

Fig. 7. Kymographic tracings show that dibenamine administered intravenously completely abolished the blood pressure response to mechanical (TBV) or electrical (EBV) stimulation of the intrathoracic vagi. A 1 per cent solution of procaine injected proximal to the point of electrical stimulation of the thoracic vagi completely abolished the normal blood pressure response.

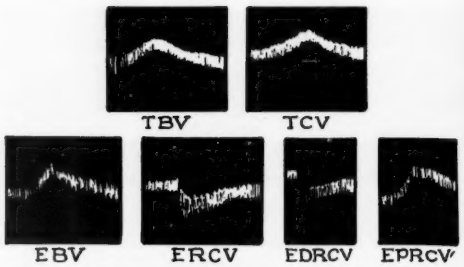

Fig. 8. Kymographic tracings show that mechanical stimulation of the thoracic (TBV) and of the cervical (TCV) vagi gives identical blood pressure responses. On the other hand, while electrical stimulation of the thoracic vagi (EBV) may give either an increase or a decrease in blood pressure, electrical stimulation of the cervical vagi (ERCV) always causes a fall in blood pressure, as does stimulation of the distal portion of the cut cervical vagus (EDRCV). Furthermore, electrical stimulation of the proximal portion of the cut cervical vagus (EPRCV) may give either a rise or fall in blood pressure.

the cut cervical vagus, there was a diminution and delay in the cardiac effects, but the heart would have stopped ultimately if the stimulation had not been discontinued. Curarization caused no diminution of the pressor response following electrical stimulation of the central end of the cut cervical vagus. Thus, while a partial block of the vagus can be produced by curare in high enough levels, there is no block of the sympathetic and one cannot count on any protection from vagal reflexes with ordinary clinical doses.

DISCUSSION

Several findings of considerable interest and importance were elicited from these studies. One of these was that traction causes a response by an entirely different mechanism than the other types of vagal stimulus. Electrical stimulation affects the afferent fibers at the point of local application of the stimulus. Traction, on the other hand, produces tension at the point at which the vagi pass through the cranial foramina. The evidence for this is as follows: (1) The response to electrical stimulation is abolished following procainization of the vagi just proximal to the point of stimulus, whereas procaine injected either immediately proximal to the point of traction or into the cervical vagi does not prevent the response elicited by traction of the thoracic vagi. (2) The type of response induced by electrical stimulation or by traction may vary in the same animal. For example, in the same animal, traction may cause an increased blood pressure whereas electrical stimulation causes a lowered blood pressure. (3) Traction on the thoracic vagi causes a marked movement or excursion of the cervical vagi, which parallels the movement of the thoracic vagi, covering a distance of 3 to 5 centimeters. (4) The vagi are neurofibrous cords without elasticity and traction applied to them results in tension at the fixed points of the nerve, mainly at the diaphragm and cranial foramina. (5) Section of the cervical vagi abolishes the response induced by traction on the thoracic vagi but traction applied to the proximal end of the divided cervical vagi gives the same response induced by traction of the thoracic vagi prior to section. Electrical stimulation may induce a diminished response following section of the cervical vagi. (6) Traction on the mediastinal or thoracic structures does not cause any significant effect. This is borne out by the above statements concerning the effect of cervical vagus section upon traction of the thoracic vagi. (7) Vagal traction in both the thoracic and cervical regions results only in blood pressure responses, whereas electrical stimulation in the intact cervical region yields marked pulse rate as well as blood pressure responses.

Another finding of interest was that the cardiovascular responses elicited by manipulation of the vagi below the hilus of the lung

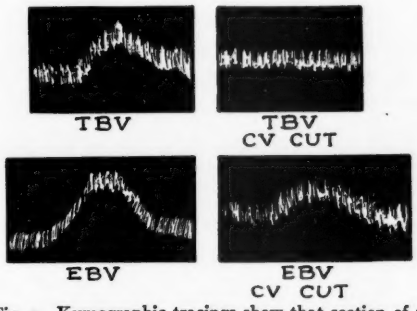

Fig. 9. Kymographic tracings show that section of the cervical vagi (CV cut) completely abolishes the usual blood pressure response to traction of the intrathoracic vagi (TBV). The response to electrical stimulation (EVC) of the intrathoracic vagi is diminished but not necessarily abolished by section of the cervical vagi.

were entirely, or almost entirely, sympathetic in nature. The evidence for this is as follows: (1) All stimuli applied to the vagi below the hilus of the lung resulted only in an elevated or lowered blood pressure; there were 2 exceptions in which there was a significant pulse rate alteration following electrical stimulation. (2) Atropine, a specific parasympathetic blocking agent, was without effect in abolishing or inhibiting the blood pressure alterations induced by vagal stimulation in the thoracic region. (3) Dibenamine, a specific sympathetic blocking agent, completely abolished all cardiovascular responses induced by vagal stimulation. (4) Procaine placed distal to the point of stimulation failed to prevent the cardiovascular responses, indicating that the impulses did not pass down the vagus nerve.

These experiments indicate that atropine in vagal paralyzing doses would be of value only in preventing a bradycardia. However, bradycardia during vagotomy could be prevented by procainization proximal to the site of vagus section.

There was no evidence that strenuous traction injured the fibers of the vagus, but this possibility does exist and should be borne in mind, especially when performing transabdominal vagotomy.

The cardiovascular responses to the various stimuli on the intrathoracic vagi were not serious and conditions promptly returned to normal immediately following cessation of the stimulation. Furthermore, there was no evi-

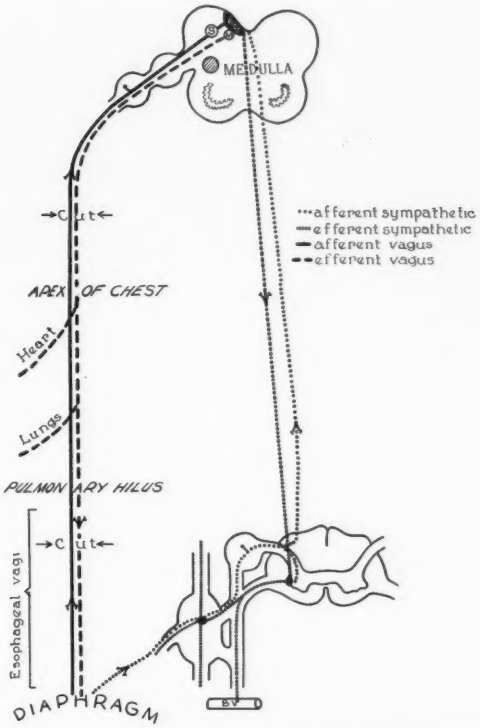

Fig. 10. Diagrammatic representation of the reflex arc involved during stimulation of the lower intrathoracic vagi. The exact course of the afferent sympathetic pathway in the cord, or whether or not such a pathway exists is not definitely known. However, persistent cardiovascular effects after severing the vagus proximally suggest very strongly that such a pathway exists; indeed no other route to the central nervous system is apparent.

dence of delayed or late cardiovascular response following release of the stimulus. In these experiments no disturbance of the respiratory or cardiovascular system occurred either during the operation or postoperatively which could explain the recorded human fatalities.

SUMMARY

From this group of experiments on the stimulation of the lower intrathoracic portion of the vagi of dogs, the following points were of significance:

1. The type of anesthetic employed during the vagotomy procedure had no apparent effect on the cardiovascular responses.

2. Traction elicited a cardiovascular response by an entirely different mechanism from that of other types of vagal stimulus.

3. Traction and electrical stimulation yielded the most marked cardiovascular effects.

4. Variation of the blood pressure was the only constant effect elicited by stimulation of the lower intrathoracic vagus. Changes in pulse rate were variable, slight and inconstant. The electrocardiographic findings were essentially normal.

5. The cardiovascular effects of lower intrathoracic vagal stimulation were mediated by afferent fibers coursing up the vagus and also through afferent sympathetic fibers up the spinal cord. The efferent arc traveled entirely through the sympathetic nervous system.

6. Local infiltration of the intrathoracic vagi with procaine solution abolished the cardiovascular responses induced by electrical stimulation, but did not affect those induced by traction.

7. Atropine had no effect in inhibiting or abolishing the cardiovascular responses induced by stimulation of the lower intrathoracic vagus.

8. Dibenamine completely abolished the cardiovascular response to vagal stimulation.

9. None of the cardiovascular effects were serious, all responses ceasing immediately following release of the stimulus.

From the experimental evidence it appears that the best way to abolish or minimize the cardiovascular responses to stimulation of the intrathoracic vagi is by gentle handling during the manipulation necessary for their resection and by the infiltration of the nerves with procaine solution proximal to the site of division. The factor of traction is a particularly important consideration when vagus resection is performed by the transabdominal route.

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PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN IN THE MACACA MULATTA MONKEY AND IN MAN

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RADICAL pancreaticoduodenectomy has not yet been proved an altogether satisfactory surgical procedure. Particularly is this true when the operation is performed for tumors primary in the pancreas. Although in a few selected series the mortality rate has been as low as 8.3 and 7.3 per cent, the average for all recorded cases continues to be in the neighborhood of 20 to 30 per cent (Table I a and b). Furthermore, the reported postoperative survival periods are short, averaging but 9 months in 71 patients with pancreatic cancer who survived operation (Table I b). Finally, out of some 150 collected cases of patients subjected to the radical operation for tumors primary in the pancreas, there are only 3 known 5 year survivors (Table I a), and the number that can be found living over 18 months numbers only 9 (Table I b).

In the New York Hospital series of 13 patients operated upon from 1941 to 1950 for cancer of the pancreas, there have been 2 postoperative deaths, 1 patient was lost to follow-up at 5 months; 4 were dead in from 4 to 9 months; 4 in from 10 to 14 months; 1 was dead at 2 years 8 months; and 1 patient has survived and is working 4 years and 9 months after operation; the average postoperative duration of life of all patients (postoperative deaths and survivors) has been 13 months. If this same figure is calculated for the survivors only, it is found to be 15 months. If the 1 long time survivor is omitted from the calculations, the average survival time of all patients is 9 to 10 months. This figure, therefore, approximates very closely that derived from the reported series. In a recent editorial Whipple (28) has indicated that radical pancreaticoduodenectomy as practiced today for primary pancreatic cancer is little more than a palliative procedure.

If the reported cases of simple biliary tract decompression for tumors of the pancreas obstructing the common duct are studied, the results obtained are on the average even worse than for the radical operation. In Table II are summarized the results obtained in over 1,000 cases in which merely palliative procedures were used. These operations yield an average survival period of 5 months for all cases (postoperative deaths and survivors) and 7.5 months for the survivors alone.

With so dismal an outlook for the patient with a malignant tumor primary in the pancreas, it seemed to one of us (CGC) that any effort that might be supposed to improve the record in this unfortunate group of individuals would be worth while. Practically each reported series of resection of the pancreas for cancer has included reference to a few patients in whom the operation has had to be abandoned because of invasion of the portal vein. In addition, there are numerous instances in which, though the operation has been completed, obvious tumor has been left behind in the wall of this vessel. When this tumor deposit has been small, partial resection of the wall of the portal vein has been successfully performed.

Furthermore, undetected infiltration by tumor of the periportal lymphatics undoubtedly occurs far more frequently than is commonly appreciated. Experiments, therefore, were started in this laboratory several years ago to determine whether the portal and

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Supported by United States Public Health Grant-in-Aid, H-167 (C), (C_2), and (C_3).

TABLE I.—RADICAL PANCREATICODUODENECTOMY

a. Summary of Radical Pancreas Operations (27)

Hospital	Pancreas No.	Papilla No.	Common duct No.	Duodenum No.	Islet cell No.	Total pancreatectomy No.	Benign lesions No.
Columbia-Presbyterian	18	22	9	7	2	7	8
10/46–10/50 24—2-8.3% mortality							
Lahey Clinic	42	26	4	7			11
In last 41 cases, 3 deaths-7.3%							
Mayo Clinic	27	17		3	1	1	
Memorial Hospital	34	2	1	7		4	
NYH-Cornell	13	6		4		1	
Total 5 year survivors	134 3						

Total postoperative deaths.....65
Total mortality.....24%

b. Radical Pancreaticoduodenectomy for Primary Pancreatic Cancer
Postoperative Mortality and Survival Period: Collected Cases

Author	No. cases	No. P.O. deaths	No. survivors				
			Total	Dead 1–9 mos.	Dead 10–14 mos.	Alive at time of report	Alive over 18 mos.
Fallis and Szilagyi	3		3		2	1 at 3 mos.	
Dennis	8	2	4			1 at 6 mos. 1 at 12 mos.	
Cole and Reynolds	4	1	3			1 at 4 mos. 1 at 7 mos. 1 at 14 mos.	
Miller et al.	27	8	19	Average survival of 13 cases was 12 mos.		1 at 15 mos. 1 at 11 mos.	4
Cattell and Pyrtek	30	5	25	Average survival of 18 cases was 11 mos.		1 at 15 mos. 1 at 12 mos. 3 less than 12 mos.	2
Bartlett	13			Average survival was 8 mos.		1 at 8 mos.	1 (?)
Parsons (23)	?	?	5	3			2
Brunschwig (3)	2		2	1		1 at 15 mos.	
Brunschwig (2)	5	3	2	2			
Harvey and Oughterson	5	1	4	2		2 at 9 mos.	
Orr	2		2	1		2 at 3 mos.	

Total cases.....99
Total P.O. deaths.....20
P.O. mortality.....20%
Total survivors.....71
Average survival period of those reported dead..... 9 mos.
Total reported surviving over 18 mos..... 9

superior mesenteric veins could be resected en bloc with the pancreas and the duodenum.

The Macaca mulatta monkey was selected for preliminary animal experiments because the anatomical relationship of the duodenum and head and uncinate process of the pancreas correspond exactly to those found in man. This is not true in the dog or cat where the pancreas occupies a mesenteric rather than a retroperitoneal position. The original experimental plan was based upon the false assumption that this monkey, even as the dog

TABLE II.—CANCER OF THE PANCREAS: POSTOPERATIVE MORTALITY AND SURVIVAL PERIOD FOLLOWING PALLIATIVE OPERATIONS (REPORTED CASES AND NEW YORK HOSPITAL SERIES, 6)

Authors	Year	Number of cases	Site of primary	Postoperative		Survivors		*Survival All cases months	Time Survivors months
				Deaths No.	Mortality per cent	Total No.	Followed No.		
·ven	1933	17	Pancreas	6	35.3	11	11	4.3	6.7
·ller and Winfield	1934	30	Pancreas	8	25.6	22	19	5.0	7.0
·dd and Hoerner	1935	94	Pancreas						10.2
·penheimer et al.	1937	30	Pancreas	11	36.6	19	14	3.9	7.0
·azer	1938	580	Pancreas	211	36.6	369	140		0–6 (92) 6–12 (34) 12–24 (5) over 24 (9)
·hey and MacKinnon	1938	47	Pancreas	9	19.1	38	38	6.9	8.6
·llinger and Kervorkian	1939	49	Pancreas	15	31.0	34	17	4.7	9.0
·llick and Garlock† (13)	1942	106	Pancreas	35	33.0	71	53	3.3	5.5
·nders and Porter	1949	50	Pancreas	4	8.0	46	30	6.1	7.0
·riestley et al.	1950	38	Pancreas		9.4				
·hild and O'Neill (6)	1951	107	Pancreas	27	25.0	80	73	5.4	7.2
		Total 1,148						Average 5.0	7.5

Calculation: Assuming a postoperative death as the shortest survival time i.e. 0, then total survival time divided by total cases gives actual average survival time. Thus in Leven survivors=11. These survived a total of 11×6.7 mos. Therefore, total survival time (73.7 mos.) divided by total number of cases (17)=an actual survival time of 4.3 months.

†These figures include exploratory laparotomies and palliative procedures.

10, 18), could not survive sudden and complete occlusion of the portal vein. It was thought necessary, therefore, if the portal vein was to be resected in the course of pancreaticoduodenectomy to drain the gastrointestinal venous bed by an anastomosis between the superior mesenteric vein and the vena cava. During one of the initial experiments, the portal vein of a Macaca mulatta monkey was so irreparably torn that this structure had to be ligated, the operation abandoned, and the animal left to die. Surprisingly enough, this monkey failed to show any ill effects of this sudden and complete occlusion of his portal vein. The next morning, he was up and about in his cage and within a few days was eating and gaining weight normally. This experiment was repeated many times (Table III) with a corrected mortality rate of 14.6 per cent. In addition, all conventional liver function tests performed during the immediate and late postoperative period failed to indicate any evidence of hepatic insufficiency. The results of many of these experiments have been reported elsewhere (5).

Emboldened by the results of these experiments in the monkey, the portal vein was similarly occluded in 4 patients (Table IV) in whom a gastric or pancreatic cancer was found inoperable due either to peritoneal implants, multiple small hepatic metastases, or

TABLE III. MACACA MULATTA MONKEY SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN

	No.	Per cent
Total monkeys	52	
Postoperative deaths	17	
Total survivors	35	
Gross postoperative mortality		32.7
Causes of death:		
Unknown	6	
Mesenteric lymphadenitis*	4	
Malnourishment†	4	
Overdose of 70 per cent diodrast	1	
Accidental ligation of hepatic artery	1	
Acute gastric dilatation	1	
	Total 17	
Corrected mortality		14.6

(Excluding animals in whom the death could be accounted for.)

*All 4 of these animals were received in one shipment and although they appeared to be in good health, they died shortly after sudden and complete occlusion of their portal vein. At postmortem examination, they all exhibited acute mesenteric lymphadenitis. No satisfactory pathological diagnosis was ever established, even though the veterinary departments of several zoos were consulted.

†These 4 animals were received in a state of severe malnutrition and should not have been operated upon.

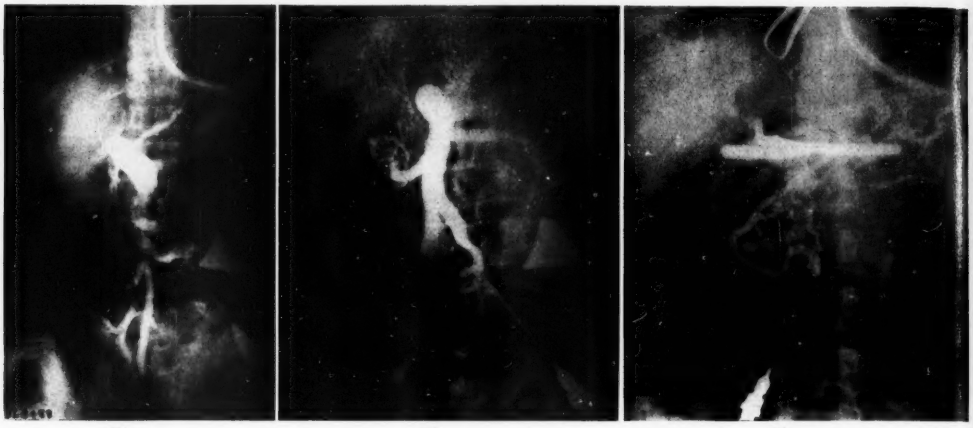

Fig. 1. Fig. 2. Fig. 3.

Fig. 1. Case 1. This roentgenogram was obtained 1 hour after sudden and complete occlusion of portal vein.

Fig. 2. Case 2. This roentgenogram was obtained 1 hour after sudden and complete occlusion of portal vein.

Fig. 3. Case 3. This roentgenogram demonstrating invasion and partial occlusion of the portal vein by pancreatic cancer was obtained 30 minutes after temporary occlusion of the portal vein.

regional lymphatic spread. The record of another such patient constitutes the case report in this article. These human patients tolerated this procedure without any untoward sequelae save, of course, for the fact that they went on to die of their original malignant neoplasm. In only 1 of these patients (Case 3) was there any evidence to indicate that the lumen of the portal or superior mesenteric veins had been compromised prior to occlusion. The portal venograms taken during the course of 3 of these operations are reproduced in Figures 1, 2, and 3.

Having demonstrated with reasonable certainty that both man and this monkey could tolerate sudden occlusion of the portal vein, it was concluded that it might be possible to resect the portal vein, the duodenum, and the pancreas in one stage. This was attempted 6 times in the monkey, and in 5 instances the animals died from blood loss before the operation could be completed. It was found quite impossible to control the extensive hemorrhage from the operative area. One animal, for some unaccountable reason, survived 24 hours.

Since the excessive bleeding which caused the death of these animals only appeared after the portal vein was occluded, one of us (GH) decided to investigate the dynamics of the splanchnic venous bed after ligature of the portal vein. In a series of 15 monkeys, the portal pressure was found to rise within 10 minutes after occlusion from the normal of 8 to 16 centimeters of saline to 40 to 60 centimeters of saline. On the day after occlusion, this had begun to fall, stabilizing within 8 to 10 days at a level of but a few centimeters of saline higher than the preocclusion level. With this information at hand, a two stage operation was designed. This proposed occlusion of the portal vein at the first stage, waiting about a week for the pressure to fall and then returning to resect the pancreas and duodenum. Such a two stage operation as this has been performed upon 23 monkeys. In the first 11 animals in this group, the pancreatic stump was closed; in the last 12 an end-to-end pancreaticojejunostomy was performed in the hope that the early high mortality rate might be reduced. The postoperative mortality has been high, and the average survival periods have been short indeed. These experiments are outlined in Table V. In this series of animals, the major problems have been concerned with the difficulties encountered in rendering even reasonable post-

Fig. 4. Portal venogram in Macaca mulatta monkey was obtained 46 days after resection of: the lower one-third of the stomach: the distal half of the common duct; the head, uncinate process, and body of the pancreas; the entire duodenum; and the upper 3 centimeters of the jejunum. The extensive venous channels developing in the pancreatic bed (indicated by arrows) and leading directly to the liver are of particular interest, for they demonstrate the enormous capacity of this animal to form collaterals.

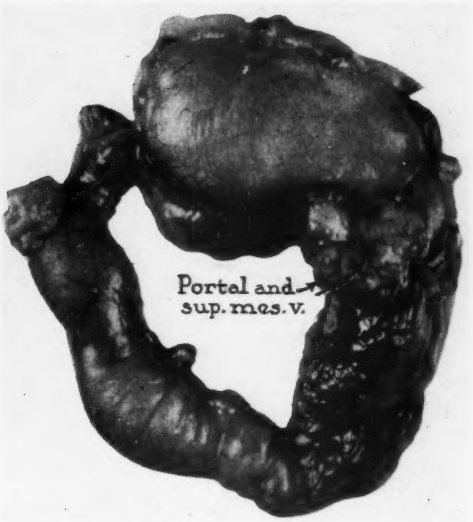

Fig. 5. Photograph of the surgical specimen in Figure 4 demonstrating the resected portal and superior mesenteric veins.

operative care. The monkeys have resisted quite successfully any efforts at gastric intubation; an infusion has required general anesthesia, and it has taken 2 strong and agile men to give them an injection of penicillin. Seven monkeys survived over 36 hours. This was long enough to reassure us that this animal was able to tolerate the upheaval in normal circulatory dynamics occasioned by resection of the portal, stump of splenic, and superior mesenteric veins. Monkey 66 survived 48 days and then succumbed in anuria 2 days after portal venography performed with 40 milliliters of 70 per cent diodrast. During his survival period, he ate well, gained weight, and did not manifest any evidence of im-

TABLE IV.—MAN: SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN

Case No.	Initials	N.Y.H. Hist. No.	Diagnosis	Date of occlusion	Portal vein compromised	Portal pressure cm. saline Pre-Post-occl. occl.	Portal venogram	Results	
								Immediate	Late
1	A.L.	368,488	Inoperable ca. of stomach	4-26-49	No		Normal Fig. 1	Transient fall of 10 mm. Hg systolic B.P.	Died 8 mos. original tumor. Liver function—normal
2	F.W.	539,941	Inoperable ca. of stomach	5-11-49	No		Normal Fig. 2	Transient rise of 20 mm. Hg. systolic B.P.	Died 2½ mos. original tumor. Liver function—normal
3	B.P.	567,794	Inoperable ca. of pancreas	5-25-49	Yes	34/34	Occluded Fig. 3	Transient rise of 40 mm. Hg. systolic B.P.	Died 3 mos. original tumor 2nd stage not done, hepatic metastases
4	F.S.	575,582	Inoperable ca. of pancreas	7-31-50	No	17/39	Normal	None	Died 4 mos. original tumor 2nd stage not done, hepatic metastases
5	M.B.	425,559	Metastatic melanoma (present case report)	5-3-51	No	12/39	Normal Fig. 6	Transient fall of 20 mm. Hg. systolic B.P.	2nd stage 5-10-51. Pt. alive and apparently well 2 mos. P.O. (see text)

Fig. 6. Case 5. Portal venogram obtained just prior to occlusion of the portal vein. Portal pressure at this time was 12 centimeters of saline. By the end of 1 hour after occlusion, this had risen to 39 centimeters of saline.

Fig. 7. Case 5. Portal venogram obtained 7 days after occlusion of the portal vein. Portal pressure at this time was 23 centimeters of saline. The collateral venous channels in the pelvis are of especial interest.

paired liver function. His portal venogram, reproduced in Figure 4 is of particular interest for the extensive collaterals which developed in the pancreatic bed. Within 40 days, this was sufficient to permit normal visualization of the liver after injecting a vein in the midjejunum with the radiopaque medium, diodrast. Figure 5 is a photograph of specimen removed from this monkey. The monkey's ability to re-establish promptly direct venous channels between the splanchnic venous bed and the liver has been completely discussed elsewhere (5).

Opportunity did not present itself to perform this operation in man for over 2 years after the initial animal experiments had been completed. Either the patients' pancreatic tumors were inoperable because of metastases or the portal vein was clearly not involved. On April 17, 1951, however, a woman 47 years old was admitted to the New York Hospital, and her portal vein was resected in two stages. Her history, physical examination, laboratory data, operative notes, and clinical course are herewith abstracted.

CASE REPORT

Two Stage Radical Pancreaticoduodenectomy with Resection of the Portal Vein for Metastatic Melanoma

M.B., NYH No. 425,559, aged 47 years, was admitted on April 17, 1951 and discharged on June 2, 1951.

History. This 47 year old housewife of Russian extraction was first admitted to the New York Hospital in October of 1945 for pain in the left arm and hand. The left anterior scalenus muscle was resected, and she was discharged improved. Two years later, she was again admitted for recurrence of pain in her left arm, and at exploration a metastatic, malignant melanoma was excised from her brachial plexus on this side.

She was admitted in 1951 because of jaundice of 2 weeks' duration. The patient stated that she had been quite well until the onset of what she considered her present illness. At that time, she developed epigastric distress after eating fatty or greasy foods. This indigestion continued for the next 2 weeks. Her appetite failed entirely, and she lost 10 pounds in weight. Two weeks before admission, her skin and sclerae became icteric, her urine dark, and her stools gray in color.

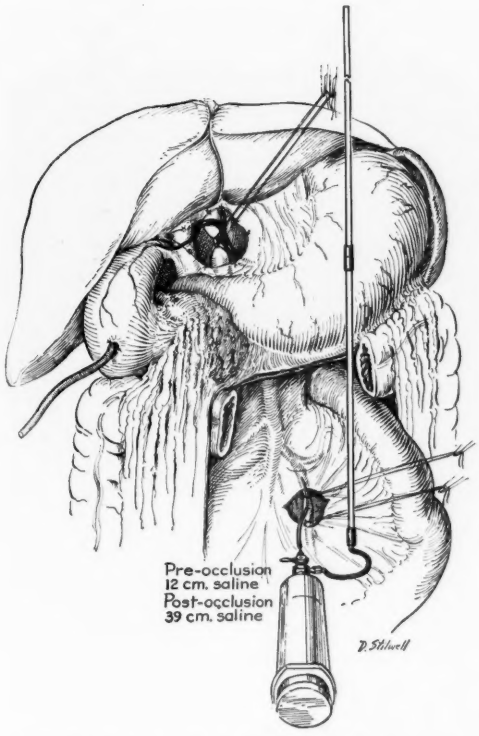

Fig. 8. Case 5. Radical pancreaticoduodenectomy with resection of the portal vein: first stage. At this operation, the portal vein was doubly ligated and a simple tube cholecystostomy performed. The polyethylene catheter for measuring the portal pressure before and after occlusion and for obtaining the portal venogram reproduced in Figure 6 is shown tied into one of the immediate branches of the superior mesenteric vein.

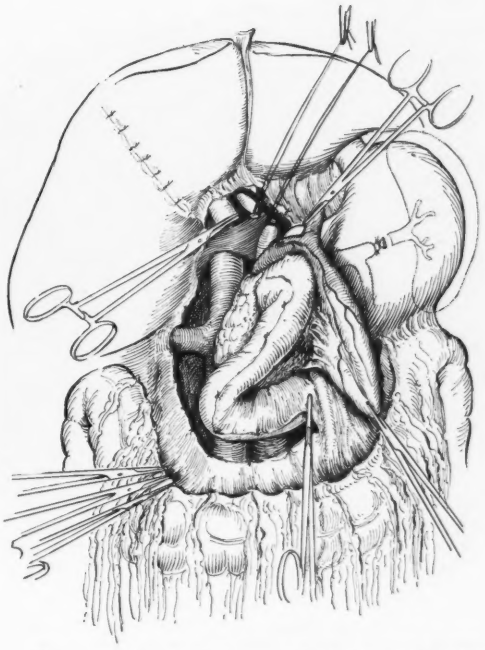

Fig. 9. Case 5. Radical pancreaticoduodenectomy with resection of the portal vein: second stage. This was performed 7 days after the first stage. By this time the portal pressure had fallen to 23 centimeters of saline. This was probably reduced another 5 to 10 centimeters by the splenectomy which is indicated diagrammatically in this illustration. The splenic vein was ligated on the splenic side of the inferior mesenteric vein. Following removal of the spleen, the gall bladder was dissected free, the portal vein and common hepatic ducts divided, and the paraduodenal peritoneum incised. As shown in this illustration, these maneuvers readily permitted dislocation of the tumor and its adnexae toward the left side of the patient.

Other than for the malignant melanoma removed from her axilla 4 years prior to her present admission and the events constituting her present illness, her history was negative.

Physical examination. This woman was well nourished, and save for her obvious jaundice appeared to be in good health. General atrophy of all muscles of her left arm and hand was present. Her abdomen was soft and flat. A mass, believed to be liver, was palpable about 3 centimeters below the right costal margin. This was smooth and nontender. The spleen could not be felt, and pelvic and rectal examinations were negative.

Laboratory data. A chest plate and bone series were negative for any evidence of metastases. A flat film of the abdomen was negative. A barium enema was negative. Gall bladder series were not performed because of her jaundice. Examination of the stomach and duodenum with barium led the roentgenologist to make a diagnosis of a neoplasm of the head of the pancreas which had invaded the distal stomach and the first, second, and third portions of the duodenum. Intravenous pyelography revealed normally functioning kidneys bilaterally. An ophthalmological consultant stated that her fundi were normal.

Her hemoglobin was 13.7 grams; red blood count, 5.3; white blood count, 13.1; 25 leucocytes; 7 monocytes; 68 polymorphonuclear leucocytes. Routine urinalysis was negative. The urine was positive for bile but negative for urobilinogen and for melanin. The stools were greenish brown and consistently positive for blood.

For complete preoperative and postoperative blood chemistry values in this case refer to Table VI.

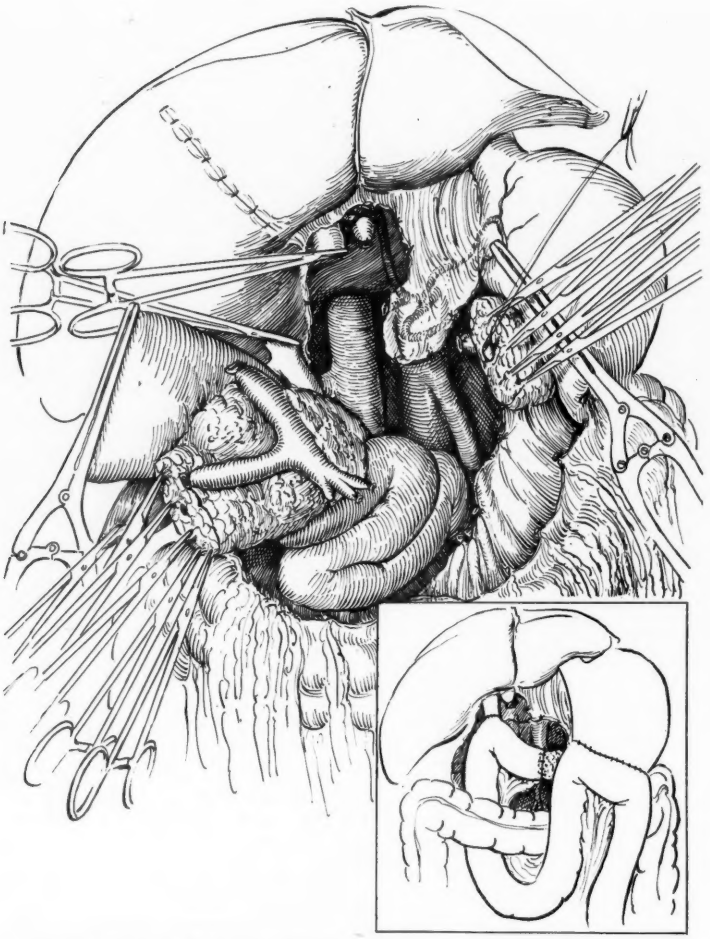

Fig. 10. Case 5. Radical pancreaticoduodenectomy with resection of the portal vein. Here the stomach and pancreas have been divided as well as the several primary branches of the superior mesenteric vein. The portal, superior mesenteric and a short segment of the splenic vein are shown in place adherent to the pancreas and tumor mass. The method of gastroenteric reconstruction is shown diagrammatically in the insert.

Course. After completing the studies recorded, the patient was subjected to the following surgical procedures.

First Stage (May 3, 1951)—Exploratory Celiotomy, Portal Venography, Ligation of the Portal Vein, Cholecystostomy

With the patient under intratracheal cyclopropane, the abdomen was opened through a generous right upper rectus muscle splitting incision. There immediately presented a large tumor mass some 10 by 9 by 7 centimeters lying within the head of the pancreas, invading the lower stomach and duodenum and adherent to the gall bladder. The entire mass was freely movable; there were no regional lymph nodes, and the liver was without evidence of metastatic tumor. A gross diagnosis of cancer of the head of the pancreas was made.

A portal venogram was performed by catheterizing a small vein in the upper jejunal mesentery with

Fig. 11. Case 5. Reproduction of a photograph of the surgical specimen, uncut. Portal vein, *P.v.*, is clearly seen.

Fig. 12. Case 5. Reproduction of a photograph of the surgical specimen, cut.

a polythene tube. Through this, 40 milliliters of 35 per cent diodrast were injected. The film obtained is reproduced in Figure 6 and was interpreted as normal. The pressure in the superior mesenteric vein was 12 centimeters of saline.

At this point, an effort was made by palpation to determine whether the tumor had invaded the portal vein. A mass of hard tissue at the lower border of the uncinate process was found to be adherent to this vessel. Although invasion was not evident from examination of the portal venogram, it seemed obvious that the portal vein was grossly involved.

Here, then, was a patient known to have 1 incurable cancer (melanoma) and almost surely having either another metastatic deposit of melanoma or at least an almost equally incurable (pancreatic) cancer. Under these circumstances, it seemed justifiable to attempt to resect her portal vein. This structure was dissected free at the porta hepatis and occluded for 30 minutes by a rubber shod Blalock clamp. During this time, her blood pressure was measured in her right brachial artery. This fell from a preocclusion level of 110/80 to 90/60 millimeters of mercury within 10 minutes. It then slowly returned to her normal level of 110/80 millimeters of mercury. When her blood pressure had stabilized at its preocclusive level, the vessel was doubly ligated, and the ends of the suture left long for ready identification at the time of the next operation. One hour after occlusion of her portal vein, her portal pressure had risen to 39 centimeters of saline.

A small tube was placed in the gall bladder and brought out through a stab wound with the hope that her jaundice might lessen while she was awaiting her next operation. The wound was closed in layers with silk.

First stage postoperative course. This patient's course following ligation of her portal vein was uncomplicated. Her temperature rose to 38.6 and 38.4 degrees centigrade during the evening of her second and third postoperative days. By the fifth, she was taking a soft diet. On the seventh, she was returned to the operating room for the second stage.

Second Stage (May 10, 1951)—Radical Pancreaticoduodenectomy with Resection of the Portal Vein for Metastatic Malignant Melanoma, Pancreaticojejunostomy, Choledochojejunostomy, and Gastrojejunostomy

With the patient under intratracheal cyclopropane, the abdomen was again opened, this time through a generous upper abdominal curvilinear

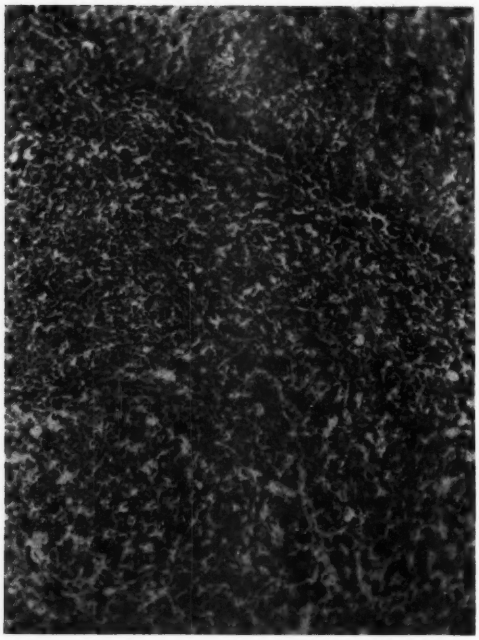

Fig. 13. Case 5. Reproduction of a photomicrograph of the tumor removed. Pathological diagnosis was malignant melanoma.

transverse incision. Portal venography was repeated, and the film is reproduced in Figure 7. This was interpreted as revealing complete occlusion of the portal vein and extensive pelvic collaterals between the capillary beds of the pelvic and inferior mesenteric veins. The portal pressure had fallen during the week to 23 centimeters of saline. Assured through evidence derived from experimental work on the monkeys that it would be safe to operate through a field the venous pressure in which was only 23 centimeters of saline, it was decided to proceed with the resection of the tumor and the portal vein. Prior to embarking upon the resection itself, however, the spleen was removed, for we believed that this could be relied upon to lower the portal pressure another 5 to 10 centimeters of saline.

The resection proper was performed in the following steps: The gall bladder was dissected free, its blood supply secured, and the common hepatic duct divided about 1.5 centimeters below the fusion of the right and left hepatic ducts. The portal vein was divided between the previously placed ligatures. The stomach was divided at the junction of its lower and middle thirds. The pancreas was transected at approximately the mid-portion of its body. Interestingly enough, the splenic vein was divided just to the patient's right of the entrance or the inferior mesenteric vein into the splenic. The entire specimen was then easily dislocated inferiorly and removed after division of the superior mesenteric vein, the inferior pancreaticoduodenal artery, the lateral duodenal peritoneum, and the jejunum at a point 5 centimeters distal to the ligament of Treitz. After removal of the tumor and its adnexae, the field of operation was dry. The enteric canal was reconstructed by a retrocolic end-to-end pancreaticojejunostomy, an end-to-side, mucosa-to-mucosa choledochojejunostomy, and an antecolic gastrojejunostomy. There was no undue bleeding in the course of performing any of these anastomoses. Two cigarette drains were placed down to the pancreatic bed and brought out through the lateral aspect of the transverse incision. The abdominal wound was closed with through-and-through silver wire stay sutures and chromic No. 00 catgut approximating the various layers of the abdominal wall. The skin was closed with interrupted sutures of fine silk. Supported by 600 milliliters of 5 per cent glucose in distilled water, 300 milliliters of 5 per cent glucose in isotonic saline, and 2,500 milliliters of whole citrated blood, this patient withstood this procedure well. Operating time was 5 hours. Figures 8, 9, and 10 illustrate the various steps in this two stage operation.

Second stage postoperative course. This postoperative period was again unremarkable. The drains were removed on the 6th and 9th days after operation. The temperature never rose above 37.6 degrees centigrade, and the serum bilirubin promptly fell to normal. She was taking a general diet by the 6th day after operation and was discharged on the 30th and 23rd postoperative days respectively with both wounds tightly healed. She returned to the out patient department 16 days after discharge where she was noted to be doing well. Her postoperative blood chemistry studies are recorded in Table VI.

Examination of the specimen. The specimen was examined by Dr. John Pearce, and his report is summarized as follows:

The specimen consists of the lower third of the stomach, the entire duodenum and upper 5 centimeters of the jejunum, the portal and superior mesenteric veins, the gall bladder and cystic and common ducts, and the uncinate process and most of the body of the pancreas. The spleen is submitted separately. Lying within the head of the pancreas and obviously involving several of the regional nodes is a tumor measuring 10 by 9 by 7 centimeters. This is yellowish white in color with several areas of dark, bluish-black. The tumor invades the distal stomach, the duodenum, the lower common duct, and the wall of the gall bladder. The portal vein is surrounded by tumor, but actual invasion cannot be identified. Upon microscopic section of numerous blocks of tissue removed from the tumor and surrounding structures, there are seen large sheets of basophilic cells whose nuclei vary widely in size and shape. Mitotic figures are scant.

TABLE V.—MACACA MULATTA MONKEY: TWO STAGE PANCREATICODUODENECTOMY WITH RESECTION OF THE PORTAL VEIN

Exp. No.	Monkey No.*	Date of		Interval (days)	Blood transfusion ml.	Antibiotics	Postop. survival	Cause of death
		1st stage	2nd stage					
1	25	11-9-49	11-15-49	6	0	0	39 hours	Acute gastric dilatation. Aspiration of vomitus
2	26	11-2-49	11-4-49	2	0	0	12 hours	Ligation of sup. mesenteric and hepatic arteries
3	27	11-16-49	11-22-49	6	0	0	5 hours	Shock (external blood loss)
4	24	11-6-49	11-14-49	8	0	0	5 hours	Shock (external blood loss)
5	31	12-7-49	12-15-49	8	0	0	5 hours	Not determined
6	37	1-31-50	2-15-50	12	150	Penicillin	48 hours	Acute gastric dilatation
7	41	2-16-50	2-23-50	7	0	Penicillin	10 days	Pneumonia. Wound infection and dehiscence
8	40	2-23-50	3-7-50	12	70	0	4 hours	Shock (external blood loss)
9	64	9-29-50	10-5-50	6	150	Penicillin	27 days	Perforated gastrojejunal ulcer. Multiple liver abscesses
10	63	10-6-50	10-14-50	8	150	Penicillin and streptomycin	12 hours	Shock (external blood loss)
11	65	10-20-50	10-31-50	11	150	0	On table	Hemorrhage from superior mesenteric artery
12	66	10-27-50	11-10-50	14	150	Penicillin and streptomycin	48 days	Anuria 2 days after portal venogram (40 ml. 70% diodrast). See Fig. 4
13	68	11-17-50	12-15-50	29	150	0	1 hour	Ligation of hepatic artery
14	73	12-1-50	12-28-50	27	150	0	12 hours	Shock (external blood loss)
15	78	12-8-50	12-25-50	17	300	Penicillin and streptomycin	17 days	Cholangiohepatitis (stricture choledochojejunostomy)
16	79	12-15-50	12-24-50	9	300	0	3 hours	Not determined
17	82	1-26-51	2-18-51	23	400	0	1 hour	Marked mesenteric lymphadenitis†
18	87	12-28-50	1-12-51	15	300	0	12 hours	Dehiscence common duct and pancreatic anastomosis. Acute chemical peritonitis
19	88	12-29-50	1-8-51	10	300	Penicillin and streptomycin	24 hours	Gangrene entire jejunum
20	95	2-2-51	2-23-51	21	300	Penicillin and streptomycin	36 hours	Dehiscence common duct anastomosis. Acute biliary peritonitis
21	124	5-18-51	5-25-51	7	110	0	1 hour	Shock (external blood loss)
22	126	6-1-51	6-8-51	7	375	0	14 hours	Acute gastric dilatation
23	129	6-15-51	6-29-51	14	350	0	18 hours	Acute anasarca (excessive i.v. fluids)

*Animals 25–95, portal vein divided at 1st stage. Animals 124–129, superior mesenteric vein divided at 1st stage.
†This animal died during an epidemic of acute mesenteric lymphadenitis in animal colony (cause undetermined).

In many areas, the tumor is necrotic while in others it is viable and appears to be actively growing. The examined lymph nodes contain much tumor. The spleen is congested. Diagnosis was malignant melanoma, metastatic.

Figure 11 is an unretouched photograph of the specimen removed at operation. Figure 12 is a similar photograph after the specimen has been cut. Figure 13 illustrates a representative microscopic section.

DISCUSSION

This is not the first case in which the portal vein has been resected. In Dr. W. Barclay Parsons' discussion (22) of the animal experiments reported by Child and his associates at the 1950 meeting of the American Surgical Association, he reported a case as follows:

"We went ahead with the total pancreatectomy plus splenectomy. Everything went splendidly until the very last point where it was quite obvious that there was extension of the tumor into the vein. We tried to do a partial resection, but that was obviously out of the question. Knowing of the two cases that

TABLE VI.—PREOPERATIVE AND POSTOPERATIVE BLOOD CHEMICAL STUDIES IN REPORTED CASE

Date	Bl urea N	Sugar	MEq./L.				Protein gms. 100 ml.				Bilirubin			Alk. phos.	Thym. turb.	Ceph. floc.	Cholesterol		Prothrombin	
			CO_2 comb. pwr.	Chlorides NaCl	Na	K	Tot.	S alb	S.glob.	Phos.	Tot.	Direct	Indir.				Tot.	Esters	Undil. dil.	Control
Preoperative																				
4/18	9	89					7.9	4.9	3.0	4.5	9.6	6.3	3.3	11.0	4.0	5.0	238	130.7	14.7 33.6	14.0
4/19											12.6	7.2	5.4							
4/24							7.7	4.2	3.5	4.0	10.9	6.8	4.1	11.3			239.5	124.5		
4/29										4.4	9.4			15.6						
5/2										3.8	10.7			12.6					15.6 37.6	15.2 39.2
Postoperative 1st stage																				
5/4 PO 1			27	100	135	4.8				3.5	16.3	9.9	6.4	10.1	6.0	5.0				
5/7 PO 4	9				122	3.0	5.9	3.4	2.5	3.9	15.7	9.7	6.0	11.1	4.0	12.0				
5/8 PO 5			27	103	128	3.7					11.6									
5/9 PO 6							6.7	3.9	2.8	3.6	12.0	7.3	4.7	8.3	5.0	7.0			14.1	15.0
Postoperative 2nd stage																				
5/11 PO 8-1		143	29	96	135	5.2					11.0						275	147.6 53.7%		
5/12 PO 9-2	8		27	95	128	5.1														
5/14 PO 11-4	8		26	94																
5/15 PO 12-5			25		133	4.6	6.0	3.2	2.8	3.1	8.7	5.7	3.0	7.8						
5/16 PO 13-6			26	93	132	4.3	5.8	3.4	2.4	4.0	6.7					7.0				
5/17 PO 14-7			29	94	136	4.9	5.9	4.0	1.9	4.0				14.1						
5/18 PO 15-8			28	93	132	4.2	5.6	3.5	2.1	4.5	4.7			10.6						
5/19 PO 16-9			28	93	127	4.8														
5/21 PO 18-10	8		25	97	129	4.9	5.6	3.3	2.3	4.4	3.3			10.7	2.0					
5/28 PO 25-18											6.5	4.1	2.4							
5/29 PO 26-19										5.4	2.4			8.1						
5/31 PO 28-21		85					7.3	4.6	2.7	4.8	1.8			9.3						

Dr. Child reported this afternoon, we went ahead with an excision of a portion of the vein. The patient has done very well, and had not a particularly stormy convalescence.

"I think the important point is that this particular patient had a partial obstruction to her vein. We didn't know enough to do some studies with injections, so we have no data, unfortunately, as to the stage of the collateral circulation that she might have developed.

"I am sure that—with the testimony of Dr. Davis and Dr. Child as to the great difference in the experimental animals—in the human being the only time when a partial resection of

the vein is possible, with life of the patient, is in those cases where there has been partial obstruction for a long enough period (and who knows how long a piece of string is?) for the collateral circulation to have started."

In 1950, Dr. E. Cooper Person and Dr. John Devine, Jr. successfully performed a one stage resection of a pancreatic tumor together with the portal vein. It was Dr. Person's impression that, even as in Dr. Parsons' case, the portal vein was partially occluded. As far as can be determined, however, the case here reported in detail constitutes the first patient in whom an unobstructed portal vein has been resected as a deliberately planned procedure. How applicable this surgical procedure is destined to become cannot as yet be decided. That it will prove of very limited usefulness appears obvious at this time. Only that rare patient with a pancreatic cancer limited to the head or uncinate process and invading the portal or superior mesenteric veins can in the forseeable future be considered a candidate for this operation.

The decision to perform the operation in one or two stages will depend largely upon whether or not the portal vein has been partially or wholly occluded. If this has occurred to a sufficient degree and for a sufficient length of time, it can be presumed that an adequate collateral circulation is present to permit resection in a single stage. Portal venography can be relied upon to provide assistance in making this decision. Study of portal pressure can also be presumed an aid. For instance, if there is evidence in the portal venogram of a defect in the portal or superior mesenteric veins and the portal pressure is normal, the portal vein should be temporarily occluded and pressure determinations made after 10 to 15 minutes. If the pressure fails to rise significantly, an adequate collateral can be anticipated and the operation performed in one stage. If, however, the pressure rises precipitously to levels of from 30 to 40 centimeters of saline, the two stage operation had best be considered the procedure of choice.

If the portal venogram is normal and there occurs a sharp rise in portal pressure on trial occlusion of the portal vein, the two stage procedure is considered imperative. Based upon experience with the one stage operation in the monkey, we believe that it is unsafe to operate through a capillary bed the venous pressure in which is much over 25 centimeters of saline.

As a side issue in these animal experiments and this two stage operation as performed in 1 patient is an item of particular interest to those having to deal with individuals manifesting portal hypertension. In each instance, the high degree of portal pressure (35 to 50 centimeters of saline) produced by occlusion of the portal vein has invariably returned to near normal levels within a week. Presumably, the cause of portal hypertension is intrahepatic or extrahepatic block. Why, then, is not a lasting portal hypertension produced in these animals? Data are far too meager, of course, to pose this question for man. Even a superficial explanation would be premature. The question is asked to stimulate thought upon the etiology of portal hypertension.

ADDITIONAL CASE REPORT

We have successfully completed another two stage pancreaticoduodenectomy with resection of the portal, splenic, and superior mesenteric veins upon a second patient. If our first case, reported in detail herein, conformed to our predictions, this case did not.

J. W., aged 67 years, NYH. No. 475,980, a negro male was operated upon for a primary duodenal carcinoma which was believed at the first stage to invade his superior mesenteric vein. Following ligation of his portal vein, the splanchnic venous pressure rose from 16 to 28 centimeters of saline. At the second stage, performed 10 days later, the portal pressure had not fallen. It was still 28 centimeters of saline. On portal venography, neither the portal, the splenic, nor the superior mesenteric vein was visualized. As the operation progressed, these were found completely filled by a firm thrombus. Although bleeding was excessive and required replacement with 4,500 milliliters of citrated blood, the operation was successfully completed through a surgical field in which the venous pressure was 28 to 30 centimeters of saline. In addition to the maneuvers described in Case 1, the upper 70 centimeters of jejunum was removed because of extensive thrombosis of the mesenteric veins in this section of gut. The patient, now 21 days after operation, is up and about taking a general diet.

Two Stage Pancreaticoduodenectomy with Resection of Portal Vein for Primary Carcinoma of Duodenum

J.W., NYH No. 475,980, male, aged 67 years, was admitted on September 12, 1951.

History. This 67 year old negro postal clerk was admitted with a chief complaint of shortness of breath of 4 months' duration. He was, however, without gastrointestinal symptoms.

Physical examination was negative.

Laboratory data. On admission, the hemogram revealed a severe hypochromic anemia and his stools were consistently positive for blood. A large ulcer was demonstrated in the duodenum upon roentgen visualization of this organ with barium. This was believed by the roentgenologist to be either a primary duodenal cancer or an ulcerating lesion secondary to carcinoma of the pancreas. The serum bilirubin was 0.5 milligram per 100 milliliters. After numerous transfusions, the patient was subjected to the following operative procedures.

First Stage (October 6, 1951)—Exploratory Celiotomy Revealing a Carcinoma of the Descending Duodenum, Portal Venography, Ligation of the Portal Vein

The peritoneal cavity was entered through a generous oblique incision extending from the left midcostal margin across both rectus muscles toward the right iliac crest. Upon opening the peritoneum there was immediately identified a napkin-ring-like tumor of the descending duodenum. The common duct was dilated to a diameter of 2 centimeters. There were no regional or distant metastases. The tumor invaded the head and uncinate process of the pancreas and upon palpation was adherent to the portal vein. A portal venogram was performed revealing dislocation and angulation of this structure toward the left. The inner border of the angulation appeared somewhat irregular. It was concluded that the portal vein was probably involved in the tumor mass. The pressure in the portal vein was 16 centimeters. The portal vein was doubly ligated at the porta hepatis. Following ligature of this vessel the pressure in the left brachial artery fell from 130/60 to 80/60. Here it remained for 10 to 15 minutes and then rose to stabilize at 110/60. Following portal occlusion, the pressure in this vessel was elevated to 28 centimeters of saline. The abdomen was closed and the patient returned to his room.

First stage postoperative course. His postoperative course was uneventful. The patient was taking a soft diet on the fifth postoperative day and was returned to the operating room on the tenth postoperative day for his second stage.

Second Stage (October 16, 1951)—Radical Pancreaticoduodenectomy with Resection of the Portal, Splenic, and Superior Mesenteric Veins. Portal Venogram, Splenectomy, End-to-End Pancreaticojejunostomy, End-to-Side Choledochojejunostomy, Antecolic Gastrojejunostomy

The previous abdominal incision was reopened and extended down almost to the right iliac crest. The portal pressure was 28 to 30 centimeters of saline and a portal venogram revealed a large number of dilated veins in and about the head of the pancreas. There was no filling of the portal, superior mesenteric, or splenic veins. Pelvic anastomotic channels, which were a feature of the first patient, were not visualized. In spite of the fact that the portal pressure did not fall and there were no pelvic collaterals demonstrated the decision was made to proceed with the operation. The spleen was removed in the hope that this would reduce the high splanchnic pressure. There was no change. The duodenum and head of the pancreas were freed laterally and the common duct and portal vein divided. The stomach was transected at the junction of the lower and middle thirds. The pancreas was divided in its mid-body. The splenic vein was divided 1 centimeter upon the splenic side of the junction of this vessel with the portal vein. The entire specimen was dislocated inferiorly and to the patient's right. After dividing the inferior pancreaticoduodenal artery and the peritoneum constituting Treitz ligament, the terminal duodenum and proximal jejunum were mobilized. At this point, as clamps were placed across the superior mesenteric vein, it became obvious that the portal vein, the splenic stump, and a good portion of the superior mesenteric veins were filled with solid thrombus. This obviously accounted for the failure of the pressure to fall and the unusual venogram. Because this thrombotic process involved all veins of about the upper third to one-half of the jejunum, 70 centimeters of this structure were resected. The proximal jejunum was passed through the defect in the mesocolon and an end-to-end pancreaticojejunostomy performed. A choledochojejunostomy was constructed in the end-to-side position. An antecolic gastrojejunostomy completed reconstruction of the enteric canal. A tube was inserted in the gall bladder and brought out through a stab wound in the right flank. The abdominal wound was closed with through-and-through silver wire stay sutures about 5 cigarette drains. These were placed down to the area denuded of peritoneum and brought out through the right angle of the wound. Because of the high portal pressure, this man lost large amounts of blood during the procedure which required 4,500 milliliters for replacement. At the closure of the abdomen, however, the operative site was dry and the patient's blood pressure and pulse were 140/80 and 86 respectively. Operating time was 7 hours.

Second stage postoperative course. This period has been quite uneventful. It is now the twenty-first postoperative day and the patient is up and about the ward and taking a general diet.

SUMMARY

1. A patient has been reported in whom pancreaticoduodenectomy with resection of the portal and superior mesenteric veins has been successfully accomplished. In so far as the authors have been able to ascertain, this is the first recorded case in which the unob-

structed portal vein has been resected as a deliberately planned procedure.

2. The experimental background for the development of this operation in the monkey and in man has been reviewed.

3. The problems inherent in either the single or two stage pancreaticoduodenectomy with resection of the portal vein have been presented and various methods suggested for their solution. The latter consist of portal venography and evaluation of the variations in portal pressure produced by trial occlusion of the portal vein.

4. The usefulness of either of these operations is admitted to be limited, at least in the forseeable future.

5. Attention has been called to the difficulties encountered in correlating the fall in portal pressure which occurs following portal occlusion with the clinical entity of portal hypertension as found in man.

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THE RESULTS OF RADICAL SURGICAL EXTIRPATION IN THE TREATMENT OF CARCINOMA OF THE ESOPHAGUS AND CARDIA

With Five Year Survival Statistics

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A SERIES of 254 patients with carcinoma of the esophagus or cardiac end of the stomach treated by radical resection and primary restoration of continuity of the alimentary canal is available for study. These patients were those who came under observation over a period of 12 years ending January 1, 1951. During this time the techniques of resection and methods of care of the patient have been developed to the point where a reasonably low operative mortality and a fair prospect of cure can be expected. So far as the immediate results of operation are concerned, these patients have had the benefit of improvements in preoperative preparation, the safe conduct through the operation, and the postoperative care which have become available for use in all types of surgical situations. The low incidence of surgical shock and the ultimate elimination of complications due to infection by means of the prophylactic use of antibiotics attest to the improvements which have developed in this field.

From the standpoint of the development of surgical techniques employed in the management of the cases, much has been accomplished although, especially in the upper segments of the esophagus, the methods of the present day leave much to be desired from the point of view of curability of the disease. In this respect it is important to recall the objectives which the surgeon must have in mind, so that the results which are obtained may be weighed correctly and the methods employed may be assessed in the light of actual experience.

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EVALUATION OF THE OPERATION AS A METHOD OF CURE (5 YEAR SURVIVAL)

The foremost aim of treatment of carcinoma in any region is obviously to eradicate the disease as the only hope of cure. To accomplish this result it has long been established as a principle that radical extirpation of the primary growth along with a wide margin of surrounding normal tissues and as many as possible of the regional lymphatic channels including the lymph nodes should be removed en masse. The importance of en bloc excision of carcinoma cannot be overemphasized. Any procedure which involves a limited excision with removal of isolated or distant lymph nodes is likely to be worthless from the point of view of cure.

The importance of this concept, long since well established as a guiding principle in the application of surgical method to the cure of malignant tumors (particularly visceral carcinoma), is exemplified in the variable results obtained in the treatment of carcinoma occurring at different levels of the esophagus. These variations bear a direct relation to the topographical relations of the various segments and the completeness with which the regional lymphatic vessels and lymph nodes can be removed en bloc with the primary lesion. For obvious anatomical reasons the success with which the ideal cancer operation can be carried out increases from the cervical area downward. *In the neck and in the superior mediastinal segment*, even though in favorable cases a safe margin may be obtained on the esophagus itself, it is virtually impossible to remove a sufficient number of regional lymph nodes in continuity with the primary growth. The results of surgical extirpation in this

TABLE I.—CARCINOMA OF THE CARDIAC END OF THE STOMACH AND LOWER ESOPHAGUS

	Prior to 1945	1945	1946	1947	1948	1949	1950	Total	Per cent of those who had opportunity to survive
Total operated upon	46	28	20	15	22	7	9	147	
Hospital deaths	8	3	2	0	3	1	0	17 (11.6%)	
Total analyzed	38	25	18	15	19	6	9	130	
Survivals at 6 months	33	21	15	9	14	4	..	96	79
12 months	23	14	13	7	7	2	..	66	55
18 months	19	9	10	3	5	1	..	47	40
2 years	13	8	8	2	4	..	..	35	30
3 years	11	5	7	2	..	..	..	25	26
4 years	10	4	6	1	..	..	..	21	22
5 or more years	8	3	..	..	..	..	..	11	17.5

group of cases are exceedingly unfavorable and they have not been included in the present report (2).

In the midthoracic region the situation is more favorable, so that if a sufficiently radical procedure is employed, a large group of nodes may be removed along with an ample margin of esophagus beyond the growth, providing the disease has not progressed too far. On the other hand, because of the proximity of vital structures including the aorta, the heart, the left main bronchus, and the inferior pulmonary veins, it may not be possible to obtain a sufficiently wide excision of the tissues around the growth-bearing segment.

In the lowermost portion of the esophagus and at the cardia, however, a more radical local and regional resection can be made including a long section of the esophagus above and of stomach below the primary tumor, much of the surrounding tissue to which the growth may become adherent, including the diaphragm and the spleen, and a large number of lymphatic vessels and lymph nodes from the lower mediastinum, the paracardial nodes, those in the gastrosplenic and gastrocolic ligaments, and especially the large group surrounding the left gastric vessels. In some instances in which the location and extent make it important, this widespread excision can be still further enlarged by removing the great omentum and all the lymph nodes along the greater and lesser curvatures of the stomach. This latter situation of course requires the performance of a total gastrectomy as a part of the procedure.

TABLE II.—CARCINOMA OF THE MIDTHORACIC ESOPHAGUS

	1944	1945	1946	1947	1948	1949	1950	Total	Per cent of those who had opportunity to survive
Total operated upon	12	18	19	21	17	8	12	107	
Hospital deaths	5	2	4	6	4	2	3	26 (24.3%)	
Total analyzed	7	16	15	15	13	6	9	81	
Survivals at 6 months	6	11	13	14	9	5	..	58	80
12 months	4	8	10	14	6	4	..	46	63
18 months	3	7	5	9	3	..	..	27	41
2 years	2	4	1	6	2	..	..	15	23
3 years	2	3	0	4	..	..	..	9	17
4 years	0	2	0	..	..	..	..	2	5
5 years	0	1	..	..	..	..	..	1	4

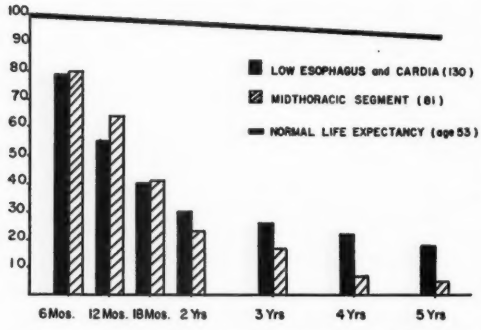

Chart 1. Relationship between percentage of survivors and location of growth at given periods after resection and anastomosis in 211 patients with carcinoma of esophagus and cardia. Abscissa—time after operation; ordinate—per cent of survivors alive.

LATE RESULTS AFTER OPERATION

The increasingly radical nature of the operation which becomes possible as the growth is found lower and lower in the esophagus is reflected in the 5 year survival rate of the patients in the series herein presented.

Tables I and II present the actual statistics for the entire series of 254 patients comprising all those who had carcinoma of the lower esophagus and cardia as group I and those who had carcinoma of the midthoracic esophagus as group II. In every case a restoration of continuity was made by primary esophagogastric anastomosis. In group II the anastomosis was above the level of the aortic arch in the majority of instances. No patients

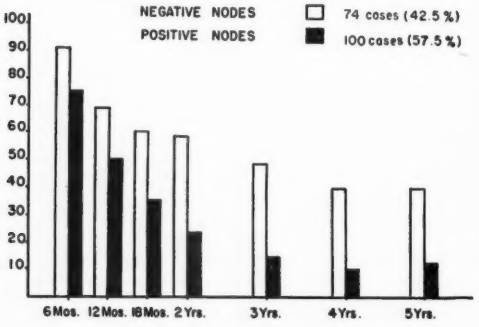

Chart 2. Relationship between patient survival and lymph node involvement after resection and anastomosis in 174 patients with carcinoma of esophagus and cardia. Abscissa—time after operation; ordinate—per cent of survivors alive.

treated by the long-since abandoned Torek procedure have been included in this series although 1 such patient, out of 12 who survived the operation, is still alive after 12 years. Comment regarding the operative mortality is made in the following. Two hundred eleven patients survived the operation, and their records are available for study.

EFFECT OF LOCATION OF THE GROWTH

The tables presented give the numbers of patients in each group per year and of those who survived from year to year, so that by a simple mathematical calculation the percentage survival of those who survived the operation at any given duration of time thereafter can be determined. For clarity these data in percentages of those alive from year to year are given in Chart 1. In this chart the patients are grouped according to the location of the growth. The effect of this factor on the end results of treatment is observed to be consistent with that which was predicted on the basis of the knowledge of the relative amount of actually or potentially involved tissue which can be removed in the two types of cases.

Thus it appears that of those patients with carcinoma at the cardia or in the lower esophagus whose operation had been performed 5 or more years before the date of this study (January, 1951) 17.5 per cent were alive 5 or more years later. On the other hand, a similar calculation reveals that of those whose growth was in the midthoracic segment of the esophagus where the possibility of extensive dissection is more limited, the 5 year survival rate was only 4 per cent. This seems to be a significant difference although the numbers of operations done 5 or more years ago (63 in group I and 23 in group II) are relatively small for statistical analysis.

One interesting observation can be made from Chart 1 which suggests that as a result of radical surgery some patients with carcinoma of the esophagus, particularly at the lower end, may be cured. This consists in a comparison of the normal life expectancy curve with the known survival curve of the group of patients studied. Chart 1 shows the life expectancy curve at age 53 (an average figure for the patient age group) based upon vital

statistics of the Commonwealth of Massachusetts. It will be observed that after 2 or 3 years of survival following extirpation, the survival curve for patients with carcinoma of the lower esophagus and cardia in particular runs almost exactly parallel with the curve of expected survival for people of a comparable age in the general population.

EFFECT OF LYMPH NODE INVOLVEMENT

It is well known that the curability of carcinoma by radical extirpation depends upon the degree of spread of the disease before the patient reaches the surgeon, as reflected in the extent of metastasis to the regional lymph nodes. In all areas it has been found that the best results are obtained in patients who have negative or uninvolved lymph nodes in the tissue removed. This series of cases shows that the same observation holds true in carcinoma of the esophagus and cardiac end of the stomach. Chart 2 illustrates the relation of the patient survival to lymph node involvement in 174 cases in which the nodes were carefully studied. It is interesting that in 57.5 per cent of the cases the nodes were involved with metastases and were apparently not involved in only 42.5 per cent of the cases. It is significant that of the 42.5 per cent of patients with negative nodes 40 per cent were alive 5 or more years after operation, whereas of the 57.5 per cent with positive nodes the 5 year survival was only 13.5 per cent. On the other hand, it is interesting and significant in evaluating the results of the application of surgical method in the treatment of carcinoma of the esophagus that as many as 13.5 per cent of those with lymph node involvement actually survived 5 or more years.

EFFECT OF HISTOLOGIC TYPE OF TUMOR

An effort was made to determine the possible influence of the histologic type of the growth upon the end result of surgical excision as based upon the survival figures. Chart 3 illustrates the results of this analysis, based upon the study of 192 cases in which an accurate histologic study was available. As will be seen, the groups are comparable as to numbers with 93 adenocarcinomas and 99 epidermoid carcinomas. The difference between the adenocarcinoma and the epidermoid carcinoma groups is so slight that conclusions cannot be drawn. The suggestion that the results may be somewhat better in the adenocarcinoma series than in the epidermoid group is in line

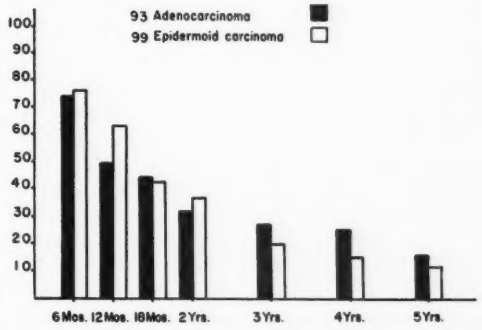

Chart 3. Relationship between histologic type of growth and end result of surgical excision in 192 patients with carcinoma of esophagus and cardia. Abscissa—time after operation; ordinate—per cent of survivors alive.

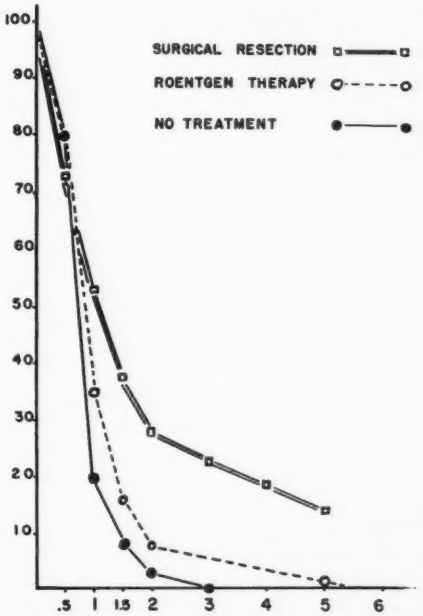

Chart 4. Duration of life in series of patients who had surgical resection compared with one of patients who had only roentgen therapy and another of patients who had no treatment. Abscissa—length of survival after diagnosis (years); ordinate—per cent of patients who might survive.

TABLE III.—AGE INCIDENCE AND MORTALITY IN 209 PATIENTS WITH CARCINOMA OF THE ESOPHAGUS AND CARDIA

Age, years	No.	Died	Per cent
Under 45	17	1	6
45–55	39	4	10
55–65	66	10	15
65–75	87	22	25

with what might be expected in view of the clinical impression that epidermoid carcinoma of the esophagus is a highly malignant tumor comparable in degree of malignancy to epidermoid carcinoma of the anal canal.

EVALUATION OF THE OPERATION AS A METHOD OF PALLIATION

In few other instances is the palliative value of an operation so important as in carcinoma of the esophagus, because of the misery experienced by the patients who ultimately become unable to swallow, often even their own saliva.

To assess the benefits of the operation from the standpoint of palliation, which is the second objective which the surgeon must have in mind, it is necessary to make comparisons with other available methods. *Bougienage* is of exceedingly temporary value, but in many instances is preferable to the employment of a gastrostomy which adds its inherent discomforts and inconvenience to the suffering which persists from the presence of the growth itself. Nowadays this method is rarely employed. *Roentgen therapy* may be offered the patient, but the results have been disappointing even with the use of high voltage apparatus (1,000,000 kv.) which makes it possible to deliver a large dosage to the growth with a minimum of damage to the skin. In a series of 97 patients with carcinoma of the esophagus treated by million volt therapy (1), satisfactory relief from dysphagia was infrequent and transitory and there was no evidence that life was prolonged significantly, even a life of suffering. Since this report was submitted, one 5 year survival has been observed after roentgen therapy in a case of carcinoma of the midthoracic esophagus. This patient died of an intercurrent disease and at autopsy no evidence of carcinoma was found although a positive biopsy of epidermoid carcinoma had been obtained before the treatment was started.

Chart 4, which shows merely the duration of life after treatment as compared with a series of patients who had no treatment except the performance of a gastrostomy for feeding, reflects the significant difference between roentgen therapy and radical surgical extirpation. It refers to epidermoid carcinoma of the esophagus excluding those located in the cervical and superior mediastinal segments.

More important than the duration of life in these patients is the fact that the dysphagia, which is the chief cause of the patient's distress, is completely relieved by surgery, whereas the swallowing function is at best only partially restored in the majority of roentgen-ray treated patients even with the benefit of supplementary bougienage. Furthermore, recurrence of tumor at the site of anastomosis is a rarity even in those who succumb eventually to the disease.

OTHER CONSIDERATIONS

Operative mortality. The mortality of the entire series of patients is 11.6 per cent for cases of carcinoma of the lower esophagus and cardia and 24.3 per cent for cases of carcinoma of the midthoracic segment. These figures include all cases, with no segregation as to the risk involved because of the age or condition of the patient, the extent of the disease, or the availability of the antibiotics to aid in overcoming infection.

It is well known that patients of advanced age do not withstand major surgery, particularly intrathoracic procedures, as well as those who are younger. To understand what influence the age of the patient imposes upon the surgeon in the management of this disease, reference to Table III is helpful. It will be seen that the actual numbers (with no correction for the percentage of those alive in the general population) increase progressively from decade to decade. This is different from the age incidence of carcinoma in other locations, where there is usually a peak incidence at approximately age 55 to 60 years. The effect of age on the mortality percentage after operations for carcinoma of the esophagus is

manifest by the observation that whereas the operative mortality at age 45 or less is 6 per cent, there is a steady increase in percentage until in the decade 65 to 75 it becomes 25 per cent.

Of the 43 deaths which occurred as a result of operation only 5 resulted from sepsis. These were all before antibiotic prophylaxis was available. Cardiac failure, including 4 cases of myocardial infarction, accounted for 22 of the deaths. Six were due to pulmonary embolism. The remainder are distributed over a miscellany of causes including pneumonia 2, atelectasis 1, chylous hydrothorax 2, infarction of the liver 1, and uremia 3. In 1 case the cause was undetermined.

Resectability of the disease. With the exception of Chart 2, which differentiates the results obtained depending on the condition of the lymph nodes, in the survival figures presented no distinction has been made between operations performed in favorable cases and those in which the disease was known (because of obvious tumor metastases inevitably left behind) to be in an incurable phase of its evolution. Because of the value of resection as a method of palliation as well as a possible cure of the disease, the original policy of removing the growth in every case in which operation was feasible has been followed consistently. The survival figures are therefore heavily weighted with the results of unfavorable cases. This policy has resulted in this series in a high percentage of resectability and operability. For example, a review of the outcome of all cases of carcinoma of the esophagus and cardia observed over a 12 year period shows that 86 per cent were operated upon and in 65 per cent it was possible to perform a resection and primary anastomosis. If the obviously inoperable cases, in which no operation was performed, are excluded it turns out that 76 per cent of the patients operated upon had a resection and anastomosis completed. These figures should be considered in relation to the fact that 57.5 per cent of the cases analyzed showed the presence of lymph node metastases at operation (Chart 2) and in only 42.5 per cent was there any actual reason in the form of negative nodes to anticipate a good result in terms of length of survival after operation.

SUMMARY

1. The results of resection and primary restoration of continuity by esophagogastric anastomosis in 254 cases of carcinoma of the esophagus and cardia during a 12 year period, ending January 1, 1951, are presented.

2. Analysis of the operability and resectability of all cases observed during this period reveals that of all patients observed 85 per cent were explored and 65 per cent had a resection performed. Of those explored 76 per cent were operated upon successfully. In the remainder a resection could not be carried out.

3. Of the patients treated by resection and anastomosis the operative mortality among those whose growth was in the lower esophagus or at the cardia was 11.6 per cent. Among those whose tumor was in the midthoracic segment, the majority of whom had an anastomosis above the aortic arch, the mortality was 24.3 per cent.

4. The fact that carcinoma of the esophagus is pre-eminently a disease of old people is pointed out as one cause of the relatively high postoperative mortality.

5. Over 50 per cent of the operative deaths were caused by cardiac failure, a condition to which old age predisposes.

6. The late survival studies show that for carcinoma of the lower esophagus and cardia 17.5 per cent of those patients who had been operated upon 5 or more years before January 1, 1951, had survived 5 or more years. For patients whose growth lay in the midthoracic segment of the esophagus the corresponding figure is 4 per cent. It is suggested that this significant difference is a reflection of the fact that for anatomical and technical reasons it is not possible to perform as thorough a regional dissection when the growth lies in the midthoracic segment as when it occurs in the lower end and at the cardia.

7. There is little significant difference in the 5 year survival rate between patients whose tumor was histologically an adenocarcinoma and those whose growth was epidermoid in character.

8. The presence or absence of lymph node metastases in the resected specimen is of definite prognostic significance. In 42.5 per cent the lymph nodes were negative. In 57.5

per cent of the cases they were involved by metastases. The 5 year survival in the negative node group of patients was 40 per cent. In the involved node group it was 13.5 per cent. These figures are based upon all the cases grouped together irrespective of the level of occurrence of the growth.

CONCLUSIONS

Resection and anastomosis provide the best method of palliation of carcinoma of the esophagus and cardia available at the present time.

Carcinoma of the esophagus can be cured (if 5 years of survival be taken as a criterion of cure) in a sufficiently large percentage of cases to make it worth while to offer the benefits of operation to every patient whose condition offers a reasonable prospect of recovery.

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TRANSDUODENAL RECONSTRUCTION OF THE BILE DUCTS

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DAMAGE to the bile ducts may result from errors in surgical technique or from an obliterative cholangitis. It is certain that many cases of obliteration of the bile ducts are not due to direct injury at the time of cholecystectomy because there is often an interval of many months between the date of operation and the first appearance of jaundice. It seems probable to us that many of these cases are due to destruction of the bile ducts by the necrotizing effect of bile that has collected in the peritoneal cavity and pooled in the region of the ducts. The necrotizing and cytolytic action of bile salts was demonstrated by Flexner and others many years ago and has been amply confirmed. Gall bladder bile in the case of the dog is particularly destructive, and the observation was made in this laboratory a number of years ago (2) that living tissues, such as spleen or kidney, when implanted into defects made in the gall bladder are much more greatly damaged than when implanted into defects in the wall of the stomach where they come in contact with the usual gastric content.

Lahey has stressed the point that the region of common duct within the pancreas usually escapes this obliterative process, an observation that we believe to be correct. This fact supports the view that damage to the ducts is due to some agent acting from without, rather than to some process acting within the duct system or to impairment of the blood supply. The extensive literature on strictures of the common bile duct and surgical methods for their repair has recently been reviewed by Cole, Reynolds, and Ireneus, and it is apparent that there is fairly general agreement that a method which utilizes the lower end of the bile duct protected by the sphincter of Oddi is preferable to methods employing direct anastomosis between the ducts and the intestinal tract.

It is the purpose of the present communication to describe a method for reconstruction of the bile ducts, making use of the intrapancreatic portion of the duct and its normal ostium at the ampulla of Vater. The details of technique are best appreciated by inspection of the drawings. The duodenum is mobilized, as indicated in Figure 1, and the remnant of hepatic duct exposed. This is often flush with the surface of the liver. The duodenum should be fully mobilized so that the pancreatic portion of the duct can reach the hepatic remnant without tension. The duodenum is then oppened, as in Figure 2, and the ampulla exposed. It is wise for the surgeon to familiarize himself both with the appearance and location of the ampulla so that it may be readily recognized. It is usually necessary to mobilize and displace the transverse colon downward to expose this portion of the duodenum. The ampulla is dilated with a graduated sound or, more simply, with a hemostatic forceps until it is large enough to admit the rubber catheter. The size of catheter employed is determined by the diameter of the hepatic duct remnant and is large enough to fit this duct snugly. The catheter is inserted through the ampulla, as in Figure 2 C, and passes upward into the pancreatic portion of the common duct which is usually present. As the catheter is pushed upward through the intrapancreatic portion of the common duct, the obstructed end is readily appreciated and can be exposed as illustrated in Figures 3 A and B. The catheter is then pushed upward until it enters the remnant of hepatic duct, as illustrated in Figure 3 C, and fixed in place with a series of interrupted fine silk sutures, Figure 3 D. The incision in the duodenum is closed, as illustrated in Figure 4, or the catheter may be led out-

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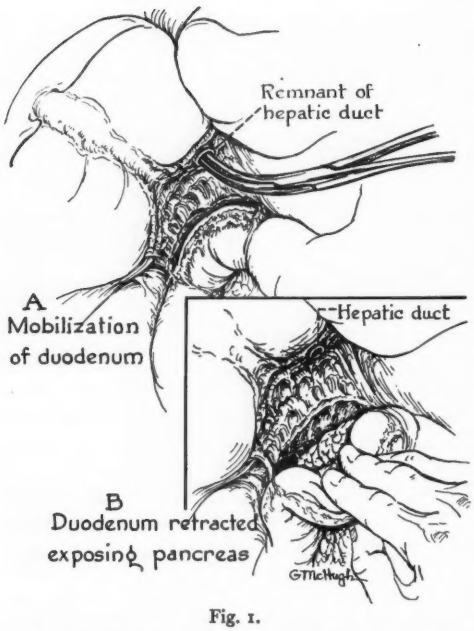

Fig. 1.

ward through a separate stab wound. It is usually wise to fasten the catheter to the duodenum at this point with a suture of chromic catgut. Omentum is then brought up and wrapped about the catheter and sutured so as to cover the incision in the duodenum. The catheter is finally led to the exterior through a stab wound lateral to the incision by the method of Wilson. A Penrose drain is placed in the region of the anastomosis with the hepatic duct and removed after 2 or 3 days. It is our practice to leave these catheters in place for at least a year to minimize the tendency for subsequent stricture at the site of the anastomosis. Ill effects from the long continued presence of the tube extending through the ampulla of Vater into the duodenum have not been seen. After a period of several weeks, the catheter may be clamped off, in which case bile escapes around the cannula through the ampulla into the duodenum. In 1 case an attempt was made to facilitate the passage of bile into the duodenum by making a small opening in the catheter shortly after its exit from the ampulla. This proved to be a mistake because the catheter became displaced outward in the immediate postoperative period and permitted bile to flow into the free peritoneal cavity, and thus a fatal, biliary peritonitis was produced.

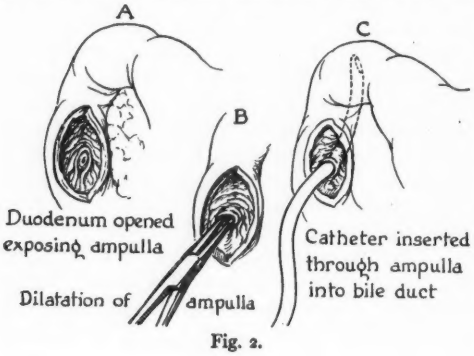

Fig. 2.

This method of reconstruction of the bile duct has been employed in 3 patients in whom the bile duct was more or less completely obliterated, and it has also been used in 3 patients with chronic relapsing pancreatitis as a method for preventing bile from getting access to the pancreatic duct. The procedure appears to be well tolerated and makes the anatomical reconstruction of the biliary duct system feasible and relatively easy.

CASE REPORTS

CASE 1. D. G., Unit Number 486645, a 29 year old white housewife, was admitted to the hospital February 20, 1950 complaining of a draining sinus of 9 months' duration. For 3 to 4 years the patient had had attacks of severe right upper abdominal pain which radiated to the back and occurred every 2 to 3 months. X-ray examination demonstrated gallstones, and in June, 1949, a cholecystectomy was performed elsewhere. Postoperative recovery was uneventful until the seventh day when abdominal distention, progressive jaundice, and clay-colored stools were noted. She was operated upon and a large abscess in the right upper quadrant was drained. Following this a fistulous tract developed and persisted, discharging profusely a bile stained material. Recurrent attacks of jaundice, pain, and distention occurred whenever the fistula ceased draining. Physical examination revealed a small, slender female with slight generalized icterus. A sinus, draining bile, was present near the upper end of a right paramedial abdominal incision scar. Routine laboratory studies of the blood and urine were normal; the serum bilirubin was 3.0 milligrams per cent direct, 3.6 milligrams per cent indirect, and the icterus index was 35. Thymol and cephalin flocculation tests were normal, and the prothrombin time was 100 per cent. On February 25, 1950 reconstruction of the

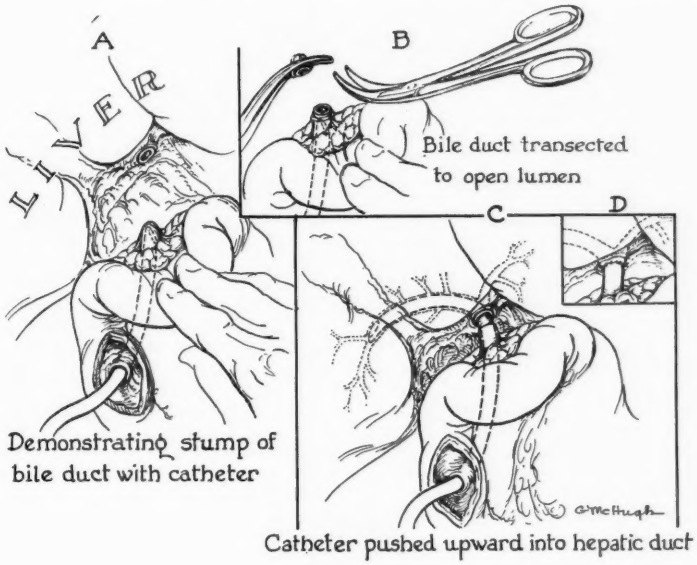

Fig. 3.

common bile duct was carried out by the technique described in this paper. The entire extrapancreatic portion of the common bile duct was absent and the dilated hepatic duct was found obstructed flush with the undersurface of the liver. A French catheter (No. 24) was passed through the ampulla of Vater, the distal end of the common bile duct, and into the hepatic duct as illustrated in the drawings. Postoperative recovery was satisfactory and the catheter was clamped off on the sixth postoperative day. The stools became pigmented and the icteric index returned to normal. She was discharged from the hospital on the ninth postoperative day. Two months after the operation she had an attack of jaundice, abdominal discomfort, and low-grade fever which lasted 3 to 4 days. Three similar attacks occurred during the following year, but otherwise the patient's condition remained excellent. On March 2, 1951 the catheter was removed, and when next seen on March 30, 1951 the duodenal fistula had entirely closed. When last seen in August, 1951 the patient was feeling entirely well and free from complaints.

CASE 2. O. J., Unit Number 429637, a 52 year old white male office worker, was admitted April 13, 1948 complaining of attacks of abdominal pain and jaundice of 18 months' duration. In 1946 the patient had an attack of severe epigastric pain associated with jaundice and light-colored stools. Intermittent attacks continued until January, 1947 when he was operated upon. Exploration of the common bile duct revealed stones which were removed and a T tube drainage instituted. Following this operation the patient remained well for about a year when periodic attacks of abdominal pain and jaundice recurred associated with dark urine, clay-colored stools, and generalized pleuritis. Physical examination at the time of admission disclosed generalized icterus and tenderness in the right upper quadrant. Laboratory examination disclosed 2+ bile in the urine, serum bilirubin 3.6 milligrams direct, 4.6 milligrams indirect, and the prothrombin time was 100 per cent. Operation was performed on April 16, 1948 and a gall bladder containing 6 small pigment stones removed. The common bile duct was opened and a stricture found at the junction of the upper and middle third. This stricture was dilated and the common

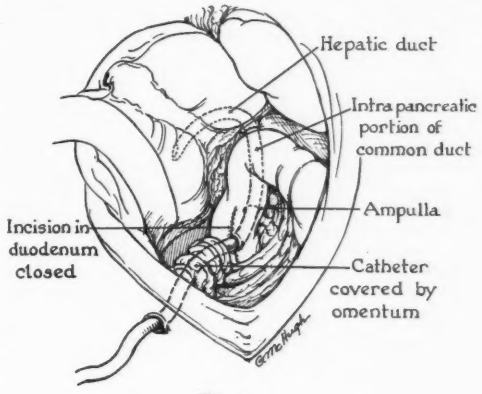

Fig. 4.

duct closed over a T tube, the distal arm of which extended through the stricture site into the duodenum. Postoperative recovery was uneventful and the patient was discharged on May 2, 1948. He remained asymptomatic, and on January 10, 1949 the T tube was removed. In June, 1949 recurrent attacks of chills, fever, and jaundice began and on April 4, 1950 the patient was readmitted to the hospital. On April 5, 1950 an exploratory laparotomy was performed. A long stricture of the common bile duct was found and excised, and reconstruction carried out by the technique described in this paper. A number of small pigment stones were found in the dilated proximal portion of the common bile duct. Postoperative recovery was complicated by a right subphrenic abscess which was drained. Following this recovery was progressive, the catheter was clamped off on April 30, and the patient discharged from the hospital on May 5, 1950. Since this time his clinical course has been entirely satisfactory. When seen on April 6, 1951 he had gained 8 pounds in weight and was in excellent general condition. In August, 1951 the catheter was removed and the patient has continued asymptomatic.

CASE 3. K. K., Unit Number 142800, a 40 year old white housewife, was admitted April 5, 1950 complaining of jaundice of 3 weeks' duration. In 1943 she first experienced attacks of epigastric and right upper quadrant pain radiating to the back following meals. In 1946 a cholecystectomy was performed and she remained free of symptoms thereafter until September, 1949 when she had an attack of abdominal pain resembling those before the operation. The attacks continued monthly until March 15 when she had a more severe attack associated with generalized icterus, clay-colored stools, and dark urine. Physical examination revealed a well developed, slightly obese female with slight generalized icterus. The abdomen revealed a well healed right paramedian scar; there was no tenderness and the liver was not enlarged. Laboratory examination revealed normal urobilinogen in the urine, the serum bilirubin was 1.7 milligrams per cent direct, 2.1 milligrams per cent indirect, the prothrombin time was 100 per cent, alkaline phosphatase 21.4 units, and the cephalin flocculation test was negative. X-ray examination revealed no radiopaque calculi. On April 14, 1950 exploratory laparotomy was performed. No stones could be palpated in the common bile duct and the pancreas appeared entirely normal. The duodenum was opened and the common duct probed through the ampulla of Vater. A stricture was encountered through which the probe could be passed with great difficulty. This stricture was dilated until a number 14 French catheter could be passed. Irrigation produced no evidence of calculi. A small hole was cut in the wall of the catheter as it protruded through the ampulla of Vater, the duodenum was closed, and the catheter brought out through a stab wound in the duodenal wall, wrapped with omentum and brought to the outside through the midportion of the abdominal wall. Postoperatively the patient's condition was satisfactory for 24 hours when she suddenly went into profound shock which was treated by transfusions of plasma and blood. The abdomen became progressively more distended and tender, and 48 hours after the operation another exploration was carried out. Generalized biliary peritonitis was found and the peritoneal cavity was lavaged and drained. The patient, however, failed to improve and died 3 hours later. Autopsy revealed that the defect cut in the wall of the rubber catheter had slipped outward until it was discharging bile into the general peritoneal cavity.

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ASPHYXIA BY TRACHEOBRONCHIAL SECRETIONS

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OBSTRUCTION of the tracheobronchial tree by mucoid secretions is discussed in practically every article on postoperative care. Recently its importance as a medical problem has been stressed (3), but from our own observation as well as that of others (3) this condition, a frequent occurrence, usually goes unrecognized. In a review of 137 consecutive autopsies, 6 deaths have occurred which can be directly attributed to asphyxia from tracheobronchial secretions. When one considers that over 61 of these 137 cases were of terminal cancer and that 5 of the 6 asphyxia deaths mentioned were not among these 61, the figure becomes even more significant. In our opinion the explanation for this high incidence of death from this condition is probably due to the poorly understood underlying pathological process that occurs. The purpose of this paper is an attempt to explain and to correlate the pathological and the clinical findings in this condition.

DESCRIPTION OF CASES

CASE 1. J. M. was a 49 year old white male who had a known history of asthma and emphysema; on February 23, 1950 he underwent a transurethral resection. Due to persistent bleeding cystoscopy was performed on February 24, under intravenous pentothal and nitrous oxide anesthesia, during which procedure he showed evidence of respiratory distress and shock, which was counteracted by blood transfusions and oxygen. Shortly afterward, on return to the ward, the patient again became cyanotic and his blood pressure dropped to 70/50. While being treated for shock the patient coughed violently and cyanosis gradually disappeared. A similar episode developed 12 hours later, at which time there was marked cyanosis and absence of breath sounds in both lung fields. Attempts at aspiration were unsuccessful and the patient expired.

Postmortem examination revealed evidence of a recent transurethral resection. The lungs were large and voluminous with crepitation throughout. The tracheobronchial tree had a large quantity of thick, tenacious mucus which almost completely filled the lumen of the bronchi and trachea, extending up to the level of the vocal cords (Fig. 1), and peripherally it could be traced into the secondary bronchi.

Microscopic examination revealed evidence of pulmonary fibrosis, thickening of the basement membrane of the medium sized bronchi, and hypersecretion of the mucus glands and goblet cells. The secretion found in the bronchi appeared to be composed mainly of amorphous material which was infiltrated with neutrophils and occasional mononuclear cells (Fig. 2). Secretion with less cellular elements was found even in bronchi of less than 1 millimeter in diameter. There was marked emphysema and some evidence of acute bronchitis. In general, the mucous lining of the tracheobronchial tree was intact.

CASE 2. A. B., a 60 year old white male with a known diagnosis of bronchial asthma for approximately 35 years, was admitted to the hospital because of cramping and tenesmus accompanied by diarrhea. The patient was disoriented, temperature was normal, respiration was rapid and shallow with a mild cyanosis being present. The chest was of the emphysematous type and breath sounds were practically unobtainable in the bases of both lung fields. An x-ray film of the chest was compatible with emphysema and congestive changes. Amebic trophozoites were found the day after admission. Aminophilline and adrenalin were administered with appreciable relief of respiratory difficulty. Throughout his hospital course, the patient coughed repeatedly, but appeared unable to expectorate any thick, mucous secretion. He expired 18 hours after admission.

Autopsy revealed the left lung to be emphysematous and the right lung partially collapsed and subcrepitant. The entire bronchial tree contained a large amount of glary, mucous secretion.

Microscopically the picture was similar to that in Case 1; however, there was more evidence of tracheobronchitis in this case.

CASE 3. J. H. was a 60 year old white male who underwent a right pneumonectomy for bronchogenic carcinoma of the right upper lobe on June 19, 1950. The patient did well until approximately 4 hours after surgery, when his blood pressure became unobtainable, pulse increased, respiration was rapid, shallow, and gasping. He suddenly ceased breathing and expired during the institution of shock therapy.

Postmortem examination revealed the absence of the right lung. Grossly the left lung revealed scattered, patchy areas of atelectasis and alternating areas of emphysema (Fig. 3). Distended lobules were prominent in some portions of the lung. On opening the tracheobronchial tree of the left lung a copious quantity of thick, bloody, mucoid material was found (Fig. 4).

Microscopic examination of the bronchi revealed no evidence of tracheobronchitis. Amorphous, pink

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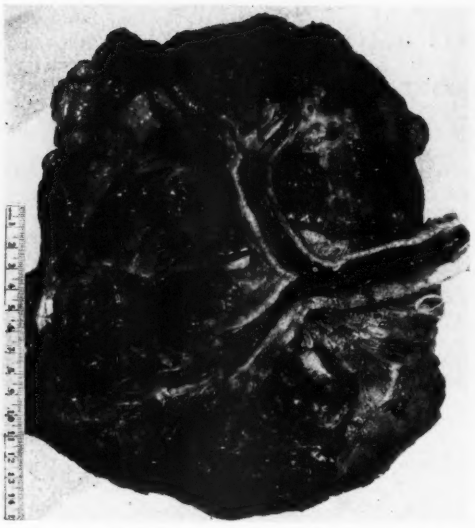

Fig. 1. Lungs showing marked tracheobronchial secretion with obstructive emphysema.

Fig. 2. Low power view showing bronchitis with secretion containing neutrophils. Hypersecretion of mucoserous glands is also present.

material was seen in the bronchi, even in those without cartilage in their walls. In scattered areas the mucus glands and goblet cells revealed evidence of hypersecretion. Emphysema was prominent and there was some evidence of atelectasis.

CASE 4. F. B. was a 58 year old white male who underwent a right pneumonectomy under endotracheal anesthesia for bronchogenic carcinoma of the right upper lobe on July 11, 1949. The patient withstood the procedure well but failed to respond following surgery. At the end of surgery the blood pressure was recorded as 90/60 and pulse 112. No note was made of respiration. The patient was kept in the operating room for about 30 minutes, during which time he received straight oxygen. He appeared stabilized and was moved to an adjoining room, where for a period of about 10 minutes no oxygen was given. The patient then experienced a violent momentary struggle and became silent. The pulse dropped to 50 per minute and the blood pressure was unobtainable. Cardiac massage was instituted after the wound was reopened, but the patient did not respond and was pronounced dead.

Postmortem examination revealed 500 cubic centimeters of bloody fluid in the right pleural cavity. The left lung was atelectatic and only an occasional area of crepitation was found. On opening the bronchial tree a tenacious, pale yellow, mucoid material was found below the level of the carina extending into all the bronchi. Cut sections revealed evidence of air only in the anterior portion of the lung.

Microscopic examination revealed marked evidence of hypersecretion of the mucoserous glands and goblet cells. Secretion, containing occasional desquamated epithelial cells but no inflammatory cells, was found in almost all of the bronchi examined, including those without cartilage in their walls. Atelectasis was prominent (Fig. 5) with an occasional area of emphysema.

CASE 5. H. R., a 77 year old white male with a history of chronic bronchitis for many years, was admitted to the hospital with a history of epistaxis of over 48 hours' duration. The red blood count was 2,810,000 with hematocrit of 28. The bleeding was controlled with anterior and posterior packs and the following day the patient received 2 blood transfusions. Although the patient coughed excessively during this period he expectorated only a small amount of mucoid material. On both July 11 and 12 the patient received 1/6 grain morphine every 4 hours. On July 12 the patient became restless and disoriented, which increased on July 13 following another dose of morphine. The chest revealed numerous moist, bubbling rales, particularly in the posterior regions. The patient expired at 7:50 a.m.

At postmortem examination both lungs were found to be voluminous and no evidence of atelectasis was seen. The tracheobronchial tree had a large quantity of tenacious mucoid material, which was found to extend to almost all bronchi as far as could be traced. Secretion was most pronounced in the posterior bronchi, but also existed to a lesser extent in the anterior bronchi.

Fig. 3.

Fig. 4.

Fig. 3. Left lung showing emphysema and patchy atelectasis.
Fig. 4. Left lung with tracheobronchial tree filled with secretion.

Microscopic examination revealed the secretion to be primarily amorphous material with only a few mononuclear cells present and was found in very small bronchi of less than 1 millimeter (Fig. 6). Evidence of longstanding lung disease was manifested by the presence of fibrosis, thickened basement membrane, and hypertrophy of the muscle fibers of the bronchi.

The following is a case of terminal malignant disease in which retention of tracheobronchial secretion was the direct cause of death.

Case 6. P. D. was a 65 year old white male who had a tracheotomy performed because of increasing dyspnea resulting from carcinoma of the pharynx. The patient was considered inoperable and treated with deep x-ray therapy. On August 5, 1950 the patient developed marked difficulty in breathing, his pulse rose to 140, his skin became cold and clammy, and his respiration was rapid and shallow. This episode was relieved spontaneously but after repeated episodes the patient became disoriented and expired August 16.

Gross examination of the lungs revealed the anterior half to be emphysematous and the posterior portion atelectatic, which findings were microscopically confirmed. The small bronchi as well as the larger bronchi contained amorphous mucoid material which was much more marked in quantity in the posterior branches, however, than it was in the anterior branches.

We have had 2 additional cases in which the accumulation of tracheobronchial secretion was diagnosed during life but this condition was not the cause of death. One came to autopsy and from the other we obtained a mucus plug as a surgical specimen. In order to differentiate these 2 cases from the previous 6 cases reviewed, we are designating them as Cases A and B.

Case A. J. L. was a 55 year old colored male who underwent surgery June 28, 1950, for a large parasagittal meningioma. Approximately 4 hours after surgery it was noted that the patient developed diminished breath sounds in his left lung field. Aspiration was carried out with a urethral catheter and some 15 to 20 cubic centimeters of a thick, tenacious, mucoid material was obtained. The patient was given atropine, and aspiration was continued intermittently until breath sounds began to come through fairly well in both lung fields. An x-ray film of the chest revealed no evidence of atelectasis. The patient did not become conscious and a tracheotomy was performed to establish an adequate respiratory airway. Aspiration was continued through the tracheotomy tube but very little material was obtained. The patient expired the day after surgery was carried out.

Postmortem examination revealed atelectasis of both lungs in their posterior segments. The remainder of both lungs was crepitant and appeared grossly normal. There was a moderate amount of thick, greenish yellow, mucoid material in the right main stem bronchus. Large quantities of this material were found in almost all of the bronchi supplying the atelectatic regions.

Microscopically, evidence of bronchopneumonia and bronchitis was found.

Case B. J. T. was a 48 year old white male who underwent a craniotomy on May 29, 1950 for a brain tumor, from which he never completely responded. Three days postoperatively the patient's respiration became shallow and rapid. Coarse, bubbling sounds were heard by merely standing near the patient. Auscultation revealed extremely poor breath sounds in both lung fields. A urethral catheter was inserted into the trachea and copious quantities

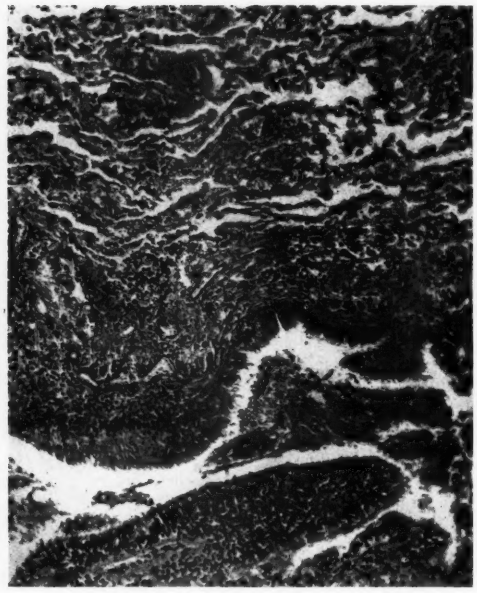

Fig. 5. Photomicrograph of lung showing bronchus containing secretion with associated atelectasis.

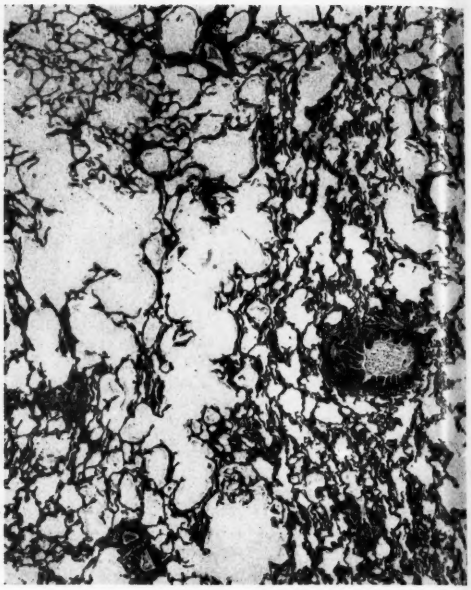

Fig. 6. Photomicrograph showing bronchus filled with secretion and associated obstructive emphysema.

of thick, tenacious, white material were repeatedly obtained. Fine breath sounds began to return to the entire right lung field and there was some evidence of return of breath sounds to the left. During this process there was aspirated a mucus plug, measuring approximately 4 by 3 by 2 centimeters and having the configuration of a bronchial cast (Fig. 7). The patient eventually deteriorated and expired July 5, 1950. No autopsy was obtained.

As may be noted from the 6 autopsy cases in which death was attributed to retained tracheobronchial secretions, a variety of conditions existed to bring about this process. Acute tracheobronchitis was found in 2 cases (Cases 1 and 2), and evidence of chronic lung disease was present in 3 cases (Cases 1, 2, and 5). Hypersecretion of the mucoserous glands and goblet cells was a prominent feature in all except 1 case (Case 3). Atelectasis was pronounced in 2 cases (Cases 4 and 6), and emphysema was prominent in 5 cases (Cases 1, 2, 3, 5, and 6).

One can only postulate as to the cause of atelectasis in Case 4. Experimentally, obstruction of a main stem bronchus of a dog takes approximately 14 hours for atelectasis to become marked (10). In a case which was reported by Brooks, complete collapse of a lobe took place 6 hours after its bronchus was occluded.

If the lung, however, is filled with oxygen, marked evidence of atelectasis can develop within a few minutes if the bronchus becomes occluded (6, 12). A high oxygen content in the lung will also mask evidence of massive collapse; when the oxygen is withdrawn symptoms will develop rapidly (12). It is also possible that a one-way expiratory valve could have occurred in the patient and could have been responsible for a rapid collapse of the lung, as has been demonstrated experimentally (8).

DISCUSSION OF PATHOLOGICAL PROCESS

On the basis of our postmortem material and a review of the literature we have attempted to explain the pathological process that takes place in asphyxia due to retention of tracheobronchial secretion. Five (Cases 1, 2, 3, 4, and 5) of the 6 patients who expired because of retained tracheobronchial secretion

had diminished lung function due to conditions such as pneumonectomy or chronic lung disease.

Perhaps with normal ciliary action and with normal quantitative and qualitative mucus, the necessity of an adequate cough reflex for removal of secretion would be diminished. But in none of the cases described here did these circumstances exist. In 3 (Cases 1, 3, and 4) of the cases postoperative conditions were present, and in 3 cases (Cases 1, 2, and 5) chronic lung disease was found. Some anesthetic agents, especially ether, are known to increase bronchial secretions (12). In chronic lung disease the cough is essential as bronchiectatic areas are frequently not lined by cilia (18); and also, mild secondary infection is probably always present. Some bacteria tend to increase the viscosity of mucus, making expectoration even more difficult (7). There was frequently a superimposed anoxic insult, such as the administration of narcotics or anesthesia, excess bleeding, and acute asthmatic attack, to an already critical state. These resulted in a diminution or absence of the cough reflex.

Without the presence of an active cough reflex the stage was set for a progressive vicious cycle which resulted in death. A depressed cough allowed secretions to collect which resulted in anoxia; this further depressed the cough reflex and in turn allowed accumulation of secretion, which resulted in further anoxia. We have found that many of these patients were kept predominantly on their backs, and due to the dependent position of the posterior bronchi, especially that of the lower lobes, secretions tended to collect in those areas. It is necessary for the cilia to move the mucus uphill in the dependent bronchi and also secretion tends to gravitate to the more dependent bronchi (2). This was borne out by a greater amount of secretions in the posterior bronchi than in the anterior bronchi as were found in the majority of cases on postmortem examination. These posterior bronchi probably become partly obstructed and obstructive emphysema then occurs, as seen in Cases 1 and 5. In these cases the respiration was apparently carried on by the anterior portions of the lungs after the occlusion of the posterior bronchi until obstructive emphysema eventually occurred in these anterior areas. If enough time elapsed, aided by hypoventilation, the air was absorbed and the posterior portions of the lungs became atelectatic. This is well illustrated in Case 6, in which the posterior portions of the lungs were atelectatic and the anterior portion voluminous.

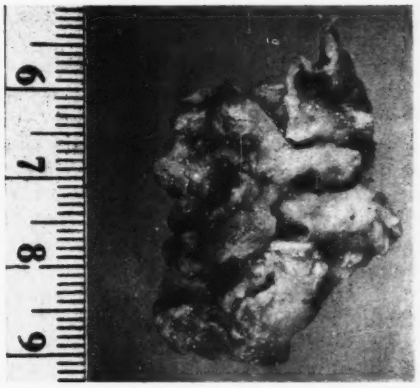

Fig. 7. Gross photograph of mucus plug removed by aspiration.

In the anterior portion of the lung, the forces of gravity probably aid in drainage but at the same time produce a reverse condition in the dependent portions. If the patient's position is properly changed it is probable that the deleterious effect of gravity would become minimal. In those portions of the lung where the drainage position was excellent other factors were present to prevent a free flow of mucus, such as in Cases 1, 2, and A, where there was evidence of acute inflammation.

Coryllos (7) pointed out that pneumococci were always present in the sputum of his patients with postoperative atelectasis. These bacteria increase the amount of fibrin and make the secretions much more viscid (4) and more difficult therefore for the cilia to expel. Although Proetz (19) has found the respiratory cilia functioning in the sinuses of cases of purulent sinusitis, there is some evidence that an acute infection paralyzes the cilia by a change of p_H (18). Furthermore, if there is any stagnation of mucus the process of evap-

oration takes place with resulting increase in viscosity. Slight changes in mucin content have a marked effect on the viscosity of mucus which will therefore interfere with its propulsion by cilia (20). We have frequently found the secretion extremely viscid. With material of this type filling the lumen one can postulate that in the process of inspiration there is dilatation of the bronchi, resulting in stretching and thinning of the mucus. This probably results in an opening in the mucus with the intake of some air. Then in the process of expiration the mucus becomes thicker as the diameter of the lumen narrows, with the trapping of air distal to the secretions. This, associated with an edema of the bronchial walls, results in the picture of obstructive emphysema. This and similar processes probably take place in many of the small bronchi as well as perhaps in those of larger dimension. We frequently found secretion within bronchi of 1 millimeter or smaller, with intact epithelium. The mucoserous glands extend out to bronchioles of 1 millimeter in diameter and the ciliated epithelium extends out to bronchioles of 0.5 millimeter in diameter (16). Potentially the process of obstructive emphysema could occur in these small bronchioles as far out as the mucous glands and goblet cells extend. If only part of a lobe is occluded, interalveolar exchange of air will keep that portion expanded until the rate of exchange becomes less than the rate of absorption (22). This interalveolar exchange of gases, plus the fact that experimentally even complete occlusion of a lobe required a period of 6 to 15 hours for atelectasis to occur (5), probably explains the necessary time requirement for the development of atelectasis.

We would like to suggest one other theory as to the immediate causes of death. In Cases 1 and 3 the patients had such large quantities of thick mucus in their trachea that it is difficult to envision the patients living as long as they did. The mucus filled approximately 50 per cent of the lumen of the trachea. It would not seem impossible, with perhaps aeration taking place only in the anterior portions of the lung, for a sudden shift of mucus to completely occlude the lumen of the functioning bronchi which would result in rapid death.

Evidence of a definite mucus plug was only found in Case B. This was a surgical specimen. Apparently enough time must elapse to allow the mucus to become inspissated. In Case B the plug was obtained on the third postoperative day.

CLINICAL FINDINGS

It is usual to expect that the patients should show roentgen evidence of atelectasis before advocating bronchoscopy. This was especially evident from the charts of Cases A and B. We would like to point out that 2 (Cases 1 and 5) of the patients who expired from asphyxia due to tracheobronchial secretions revealed no evidence of atelectasis. Two others (Cases 2 and 3) showed only slight evidence of atelectasis, and only 1 patient (Case 4) had marked evidence of atelectasis. Four cases (Cases 1, 2, 5, and 6) revealed marked evidence of obstructive emphysema. The absence of atelectasis, therefore, cannot be considered as indicating unobstructed bronchi. One of the earliest and important signs in retained secretion is the presence of a nonproductive cough. This was described in Cases 2 and 5, but the significance was not recognized.

The presence of rhonchi is also one of the earliest findings and is due to the accumulation of secretion. As obstruction of the bronchi progresses, breath sounds become diminished. Due to the presence of obstructive emphysema, which is frequently found, one should not expect to note percussion signs of dullness. As anoxia progresses, cyanosis and dyspnea develop. Disorientation due to cerebral anoxia and restlessness are not uncommon. The presumptive diagnosis can be confirmed by aspirating material with a catheter. Haight (14) suggests that when a patient is unable to ventilate the bases of his lungs on deep breathing, the presence or absence of rhonchi should be determined by auscultation during hyperventilation with carbon dioxide.

TREATMENT

From a review of the charts in these cases and the literature, several facts became apparent. Removal of the secretions almost immediately relieves the patient (10). Aspiration has been recommended by many authors (3,

13, 21). Usually a No. 16 or 18 French urethral catheter is advocated. Some (9, 21) have suggested that the tip of the catheter will be well inside the stem bronchus when 3 or 4 inches of tubing are still outside the external nares. We carried out this procedure on several cadavers and opened the trachea in situ. We then tested the catheter for slack. Frequently it was necessary to insert the catheter until only an inch remained outside of the external nares before the tip of the catheter was well in any of the branches of the main stem bronchus. In 1 cadaver, height 6 feet 2 inches, the tip of the catheter only went the length of the main stem bronchus when it was so inserted that less than an inch remained external to the nose. The depth of insertion and, therefore, the adequacy of aspiration vary with the length of the trachea of the patient, and the length of the tubing. This experiment, however, should not detract from the value of aspiration. Frequently it is the only procedure necessary, especially if it stimulates adequate coughing.

It would probably be wisest to bronchoscope without hesitation those patients who did not immediately respond to aspiration. From our experiments with catheters on cadavers, bronchoscopy should be far more effective and complete. One author stated that he bronchoscoped a patient twice a day for 4 days without harmful effect (21). Atropine has been advocated and was used in Case A. Several authors (4, 14), however, have suggested that atropine, although decreasing the amount of secretion, increases the viscosity. Any drug which tends to increase the tenacity of the secretion, therefore, makes its expulsion more difficult and should be contraindicated.

Postural drainage has been frequently advocated. It might be well to point out that Galloway states that with elevation of the feet at an angle of 20 degrees, the main stem bronchi and trachea are only horizontal. For adequate drainage therefore the patient's Trendelenburg position should be over 20 degrees.

Frequent changing of the patient's position for the prevention of accumulation of secretions and thus the formation of atelectasis has been advocated. Not uncommonly we have seen the patient's position changed by pillows under one shoulder (this occurred in Case A), but in this process only elevating the chest to a 30 or 40 degree angle with the bed. It should be pointed out that unless the patient is placed on his side at a 90 degree angle some of the posterior bronchi will remain in a dependent position. Coryllos (4) believed that carbon dioxide loosened the viscosity of the thick bronchial exudate and transformed it into a thin, frothy secretion. This has been further confirmed by later authors (15). It has been pointed out (9) that carbon dioxide produces bronchial dilatation. Therefore, if carbon dioxide is used therapeutically to help remove tracheobronchial secretion, the patient should be in an adequate position for drainage if he is unconscious (9).

Steam inhalation has also been used to aid expectoration of secretions. It apparently produces, however, an output of respiratory fluid from major bronchi rather than from finer ramifications (17). Steam (17) combined with carbon dioxide (15) has been recommended for prevention of dryness, especially when oxygen is used.

SUMMARY

In a review of 137 consecutive autopsies we have found 6 cases in which the cause of death was directly due to asphyxia from tracheobronchial secretions. The mechanism of the process appeared to have been that of various insults to the respiratory system until a depression of the cough reflex occurred. When the cough reflex became depressed a vicious cycle was produced, in which secretion was retained and further depression of cough resulted in greater retention of secretion. This process finally resulted in death. There were 3 postoperative cases, 1 transurethral resection, and 2 pneumonectomies. One patient had carcinoma of the pharynx. Evidence of chronic lung disease was present in 3, and acute tracheobronchitis in 2 cases.

From a clinical standpoint it is interesting to note that emphysema, probably on an obstructive basis, was prominent in 5 cases, and atelectasis was pronounced in only 2 cases. In 2 cases in which obstructive emphysema was very pronounced no atelectasis could be found.

A review of therapy and an experiment with urethral catheters conducted on cadavers are also presented.

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MYOLYMPHANGIOPLASTY FOR THE PREVENTION AND RELIEF OF THE SWOLLEN ARM

A Preliminary Report

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SINCE its inception, radical mastectomy has been followed by a not infrequent complication—the swollen arm. Known under a varied nomenclature, it has been called the lymphedematous forearm, the brawny arm, and more formidably, elephantiasis chirurgica. By whatever term it is called, its presence immediately connotes a condition that is distressing physically and mentally to its possessor, disturbing and possibly alarming to the surgeon. Among the persistent queries of the patient most frequently asked before the operation is "Will I have a swollen arm?" After surgery if the arm swells, and it does to some degree in 70 per cent of the cases, the patients repeated questions are: "Will my arm remain swollen?" and "Will it get worse?" Still further is the request to alleviate or eradicate the complication. And what surgeon would not be willing and eager to reduce the swollen member to the preoperative size.

By physiotherapeutic measures—posture, massage, and bandage—attempts have been made to achieve a reduction in swelling. These means accomplish a transient result. Then a surgical attack may be next, unless an inoperable recurrence, fibrosis from infection or radiation or previous surgical attempts preclude it. If none of these complications are present, then the operative approach seems warranted. But for the most part all the surgical methods heretofore have ended in failure, though the immediate results may have appeared satisfactory. The number of operations proposed in the past bear witness to the fact that no single surgical therapeutic measure has been developed to cope with the complication. There is possibly one exception and that is the use of gelfoam laminated rolls to be reported by the author shortly. The procedures previously advanced may be enumerated and grouped as follows:

1. Operations utilizing methods for increased return flow of subcutaneous lymph by providing new channels.
   a. Kondoleon's operation.
   b. Lymphangioplasty (Handley).
   c. Beck's operation.
2. Skin pedicle fusing the arm with the chest wall or tube pedicle from the posterior chest wall to the arm.
   a. Standard's operation.
3. Resection of the axillary vein.
   a. Neuhof's method.
   b. Macdonald's method.
4. Paravertebral block—stellate ganglion.
5. The use of a homologous muscle transplant as a part of the radical mastectomy.
   a. The pectoralis muscle is used to surround the nerve artery and vein.
      1. Murphy's method.
      2. Peck and White's method.
   b. The latissimus dorsi muscle is used to obliterate the apical axillary dead space.
      1. Rienhoff's method.
      2. Hutchin's method.
   c. The use of the teres major muscle.
      1. Treves's method (under report).
6. The use of gelfoam rolls.
   a. Treves's method.

As we have heretofore, we again wish to emphasize that the solution to the problem of the swollen arm is prevention. Once its presence is firmly established, there is no satisfactory method to correct it with the possible exception of Standard's method. This so restricts the motion of the arm that the amelioration of the condition by the operation seems vitiated.

For this reason surgeons have been constantly aware of the necessity for providing a means to prevent the complication. At the time of the radical breast operation all measures should be employed to minimize infection,

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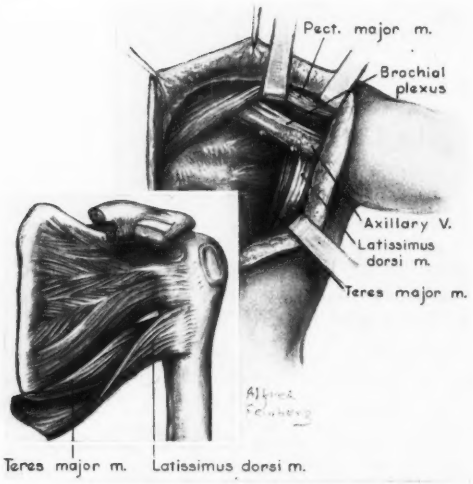

Fig. 1. The axilla at the completion of the radical mastectomy. The remaining portion of the pectoralis major muscle has been retracted. The relationship of the teres major muscle to the latissimus dorsi muscle is semischematic. The insert shows the origin and insertion of the teres major, posterior aspect.

prevent slough of the skin edges, obliterate the axillary dead space, and reduce the formation of drainage or more properly provide for continuous and complete evacuation of blood serum, liquefied fat, and lymph. Of prime importance is the institution of measures to prevent angulation of the axillary vein. While

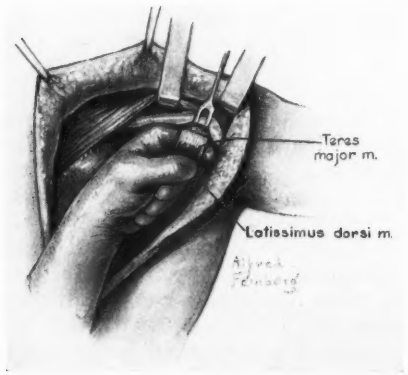

Fig. 2. The pectoralis major and latissimus dorsi muscles are retracted. The index finger lies behind the belly of the teres major muscle. The dotted line indicates the line of division of the muscle through its tendinous insertion.

no figures are available on the incidence of thrombosis of the axillary vein, this condition must occur more frequently than is surmised. The occasional immediate postoperative appearance of the swollen arm, suffused and of a purplish hue, must indicate that venous obstruction has been produced by thrombosis, acute angulation of the axillary vein, or constriction of the axilla by too snug a surgical dressing.

In 1948 we reported a heretofore unrecognized and unreported sequel that ensues in an edematous upper extremity that has developed following radical breast surgery but long after the malignant breast neoplasm has been arrested. This is a new specific tumor —lymphangiosarcoma. This lesion arises in lymphatics, the site of chronic obstruction, which chronic obstruction has been the sequel of radical mastectomy.

One reason for the obstruction, that at least concerned chronic lymphatic occlusion, was as follows:

It appears that following radical mastectomy, a moderate degree of fat necrosis occurs at the upper angle of the mastectomy scar. The entire fat layer is subsequently replaced by a fibrosis that continues down to and around the nerve, artery, and vein and is especially marked about the first portion of the axillary vein. Here a fine band of scar tissue not only compresses the vessel but also acts as a sclerotic barrier to the deep lymphatics surrounding the vein. These lymph vessels, the brachial lymphatics that take their origin in the nodes of the cubital fossa, are well illustrated in Rouvière's anatomical description. They form the deep collecting trunks of the arm, continuing the deep trunks of the forearm, are two or three in number, and accompany not only the brachial vessels but the profunda brachii as well. They terminate in the axillary nodes where they are interrupted by axillary dissection. It is in this region, but mesial and inferior to the insertion of the pectoralis major muscle, that this constricting band of scar tissue may be observed, and it is our opinion that this may be the locus of obstruction.

Be that as it may, it is obvious that a heretofore unrecognized hazard exists for the

patient with breast cancer. Conservatively speaking some degree of swollen arm supervenes after radical mastectomy in about 70 per cent of women. This group constitutes the candidates for lymphangiosarcoma. Until this lesion is recognized as a clinical entity and ceases to be confused with recurrent mammary cancer, one cannot know its frequency and how great a hazard it may be.

Not only does lymphatic obstruction bear directly on the problem but (1) reflex spasm of blood vessels, (2) angulation of the axillary vein that not only causes venous stasis but interferes with the return flow of lymph in the blood vessel walls, and (3) cicatrization of the axilla are concerned individually or collectively as causative factors. To obviate these conditions, it would seem that the best approach would be to prevent their occurrence postoperatively by some procedure combined with the radical mastectomy. To prevent angulation of the axillary vein and to provide a viable homologous tissue covering that would splint it, to provide by the same procedure tissue that would protect the axillary contents from a cicatrix and obliterate the dead space in the apex of the axilla, and lastly, to supply by this tissue a viable bridge along which the severed profunda lymphatics could regenerate and re-establish continuity, these measures would seem highly desirable. As a method for fulfilling these desirable criteria the one here reported was developed.

OPERATIVE TECHNIQUE

The usual radical mastectomy with axillary dissection is performed. After ligating all bleeding points, the operative field—especially the chest wall—is covered with warm moist laparotomy pads. The axilla is left exposed. The insertion of the teres major muscle is identified and divided, care being taken to avoid injury to the musculospiral nerve either directly or by prolonged pressure from retraction necessary to expose the tendinous insertion of the muscle (Fig. 1). The tendinous portion is held by a serrated clamp and turned mesially bringing the muscle anterior and cephalad. This change of direction of the muscle helps to obliterate the dead space in the apex of the axilla and provides a splint and

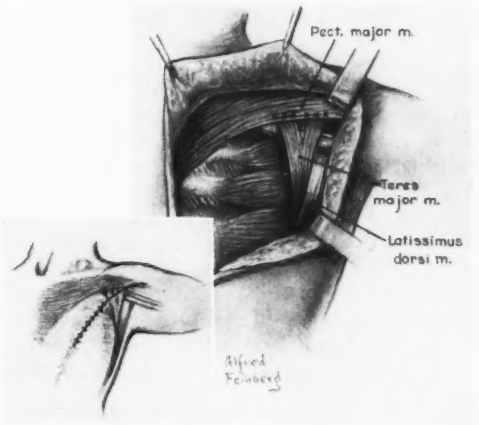

Fig. 3. The tendinous end of the teres major muscle is attached to the inferior edge of the pectoralis major muscle by interrupted mattress sutures of black silk or kangaroo tendon. The belly of the muscle is often divided and forms a Y. If long enough, the mesial border is tacked to the intercostal muscles by similar sutures. The insert shows the schematic anatomical relationships at the close of the operation.

sling for the axillary vein (Fig. 2). The origin of the muscle is then attached to the inferior surface of the cut margin of the remaining portion of the pectoralis major muscle, mattress sutures of fine kangaroo tendon or medium silk being used. The inferior edge of the teres major may be tacked to several of the intercostal muscles by similar sutures, if the muscle

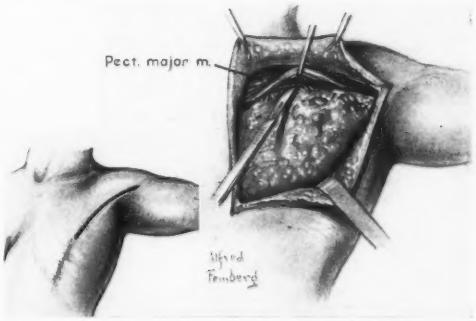

Fig. 4. Insert shows the incision line through the previous radical mastectomy scar, the approach to the operative exposure of the axilla in an attempt to relieve the swollen arm. Dissection shows the freeing of the border of the pectoralis muscle and the underlying fat and axillary scar. The effort to relieve the swollen arm by this method has since been temporarily distconinued.

is long enough and not too taut after it has been anchored into the margin of the pectoralis major muscle (Fig. 3).

The muscle so placed overlies the vessels and is a barrier to any cicatrix that may form. Its lateral border is contiguous to the severed profunda lymphatics. It is by this muscle pathway that the lymphatic vessels may regenerate along a homologous living tissue bridge from the forequarter to the chest wall.

The success of this procedure is predicated upon the survival of the muscle. Anatomically, the blood and nerve supply to the muscle is not interfered with by the division of the muscle at its insertion. In fact, they are definitely preserved. The muscle at the completion of the procedure maintains its normal color. Division of the muscle does not seem to interfere with the normal function of the shoulder. Whether it ultimately survives is impossible at this time to state, since no axilla in which this operation has been carried out has been reopened.

We may state that as a corrective therapeutic measure, once the swollen arm has developed, this procedure has proved of no value in the cases in which we have tried it (Fig. 4). In 2 instances the scarring in the posterior axilla was so dense that the muscle could not be mobilized. In 3 other cases in which it could be freed, the initial result was satisfactory, but the lymphedema eventually returned. As a secondary operative procedure one finds that the teres major muscle is in a bed of the axillary cicatrix and when freed is usually shorter and certainly less pliant than when it is dissected out at the time of an initial radical operation. For this reason we have discontinued myolymphangioplasty as a corrective therapeutic surgical attack on the postoperative lymphedema following radical mastectomy.

RESULTS

We have used this operation in 10 cases as a part of the original attack on breast cancer. That is, myolymphangioplasty has been employed for prophylaxis against the occurrence of elephantiasis chirurgica. From these few instances we feel that the procedure has merit and its inclusion as part of the radical breast operation should be carried on. We discontinued its use temporarily when we began the use of gelfoam laminated rolls to prevent the swollen arm. The eventual success of either method will determine which of the two will become the standard procedure.

SUMMARY AND CONCLUSIONS

The operations heretofore employed for combating postoperative swelling of the forequarter following radical mastectomy have been summarized.

The major causes that may initiate the process have been recounted.

A lethal sequela of elephantiasis chirurgica, lymphangiosarcoma, has been re-emphasized.

A method has been reported that utilizes living muscle tissue to prevent the swollen arm by occluding the axillary dead space, splinting the axillary vein to prevent angulation and scarring of the axilla with subsequent stenosis of the vein, and finally providing a homologous tissue bridge over which regenerated deep lymphatic vessels might grow.

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THE CYTOLOGIC INTERPRETATION OF THE PROSTATIC SMEAR

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THE early diagnosis of carcinoma of the prostate still remains a challenge in medicine. The disease seems to remain silent for an unknown period of time until the onset of symptoms only too often reveals an already far advanced disease. At present the curability of this cancer depends on its early discovery and complete surgical eradication. Any aid, therefore, that can lead to an early diagnosis will be worth while to investigate. The cytologic interpretation of prostatic secretion has proved to be of great value, as the desquamated cells give certain information about the epithelium of the organ from which they originate. This study reports the cell types found in prostatic smears under varying conditions of the prostate.

A first discussion of cells found in expressed prostatic secretion was given by Mulholland in 1931. His description of cells, found in the secretion of patients who had carcinoma of the prostate is eloquent and it is astounding that this method of examination remained unused for many years. It was not until several years after the standardization of the cytologic technique by Papanicolaou, that Herbut and Lubin described the identification of cancer cells in the prostatic smear. Since then several investigators have stressed the applicability of the prostatic smear examination to the diagnosis of cancer of the prostate (1, 3–7, 10–14), whereas one investigator (2) doubted its reliability.

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This investigation was carried out in the laboratory supported by the Monroe County Branch of the American Cancer Society.

The survey of the prostatic smear gives an insight into cells and cell changes of the prostate itself as it contains cells from all those parts of the prostate which are connected with the urethra by patent ducts. In addition, the smear prepared from this expressed material will contain cells desquamated from the urethra, seminal vesicles, and the ampullae.

METHOD

Secretion obtained by prostatic massage is placed on a glass slide on which a thin film of Mayer's albumin has been spread to insure adherence of the material. A second glass slide is placed on top of the first one and the two are pulled apart. Both slides are dropped quickly, before the material has a chance to dry, into a bottle filled with equal amounts of 95 per cent alcohol and ether. After fixing for an hour or more, they are stained with Papanicolaou's staining procedure.

CELL TYPES FOUND IN SMEARS COMING FROM NONCANCEROUS PROSTATES

The secretion expressed from the prostate of a healthy young person contains few cells (the scant smear). A smear made of such a secretion shows only an occasional rather small cell which on low power survey is easily overlooked or mistaken for a leucocyte. They are columnar cells measuring 5 to 6 micra. The round nucleus occupies up to two-thirds of the cell. It appears homogeneous without any recognizable chromatin structure. The

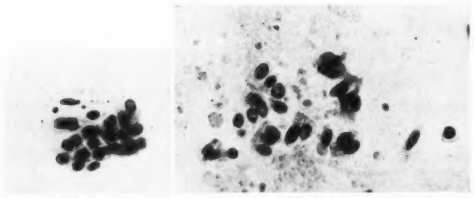

Fig. 1. Fig. 2.

Fig. 1. A loose group of columnar cells in prostatic secretion. ×300.

Fig. 2. Single columnar cells with well preserved cell membranes. ×300.

cytoplasm stains lightly pink. Some leucocytes are seen in these scant smears but other epithelial cells are conspicuously absent.

The prostate of older men usually desquamates columnar cells freely (the abundant smear). In the smear they are seen singly, in loose groups (Fig. 1) or in small sheets. Cell membranes are usually not recognized in cells seen in groups but are preserved in those lying alone (Fig. 2). The cytoplasm is acidophilic. The nuclei commonly measure about 6 micra, but their diameter may vary from 3 to 9 micra. They are larger than the nuclei of the columnar cells found in the scant smear. The nuclei stain lightly and uniformly blue. The nuclear membrane, which is distinct and rather heavy, stains deeply and thereby accentuates the pale nucleus. A small nucleolus may be clearly visible in some cases, however, this is usually absent.

Columnar cells are found in great numbers in smears obtained from patients who have benign prostatic hypertrophy (Fig. 3). Their nuclei show some variation in size and tend to be larger (6 micra to 10 micra), stain pale blue and contain a fine granular chromatin network. At times one or two small nucleoli (1.2 micra) can be distinctly recognized in the delicately stippled nucleus. The columnar cells of the smaller variety with their uniform pale nuclei are mixed with these larger cells which gives the smear a rich varied appearance.

Prostatic concretions (corpora amylacea) are found in the prostatic smear. They are pink, round or oval bodies and distinctly laminated. Cells desquamated from the epithelium of the urethra are occasionally found in the smear. They are most commonly seen as single large polyhedral cells (about 25 micra), but occasionally are shed in small groups (Fig. 4). Their cytoplasm is acidophilic. The centrally placed nucleus is either vesicular and fairly large (10 micra) or small and pyknotic.

Histiocytes in the prostatic smear as in other media are found in a large variety of sizes and shapes. The large histiocyte is most easily recognized. Often mixed together with other cells, it stands out clearly from its surroundings (Fig. 5). Its shape is irregular and variable. The ample cytoplasm, which stains a pale pink, is foamy or shows large vacuoles.

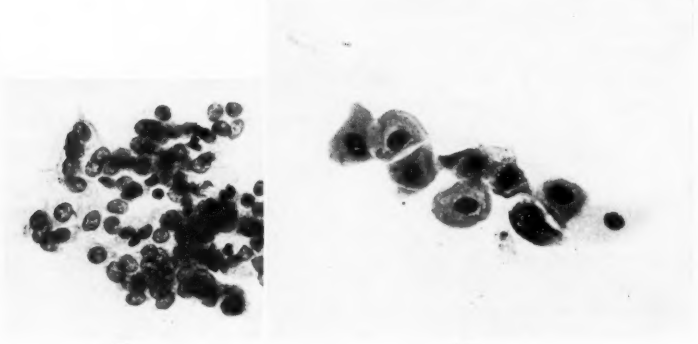

Fig. 3. Fig. 4.

Fig. 3. Columnar cells with pale staining nuclei and distinct nucleoli. Clinical diagnosis: benign prostatic hypertrophy. ×325.

Fig. 4. Cells desquamated from transitional epithelium.

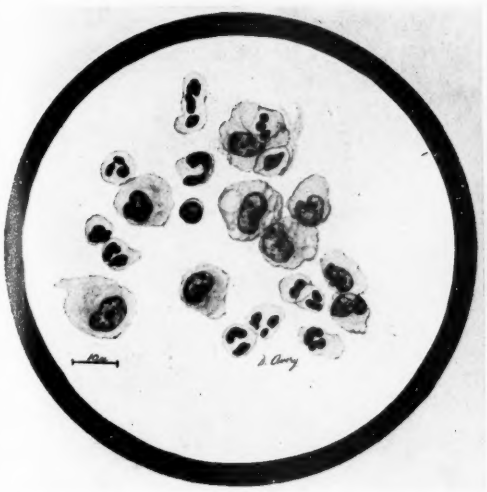

Fig. 5. Histiocytes in prostatic secretion. Camera lucida drawing. ×655.

Fig. 6. Group of degenerated cells, histiocytes, leucocytes. Camera lucida drawing. ×440.

Its phagocytic property can clearly be seen when leucocytes, degenerating cells or other debris are found in the vacuoles. The nucleus is eccentrically located and often indented. Its size varies greatly with the size of the whole cell. Nuclei from 5 to 10.5 micra may be seen within the same cell group. The chromatin structure can be fairly dense but more often is seen in fine granules. Rarely is there any hyperchromasia. Nucleoli often appear quite prominent and can be multiple, their size rarely exceeding 1.3 micra. Histiocytes are found abundantly in material coming from the infected prostate. In such smears dense groups are seen consisting of degenerating and degenerated columnar cells mixed with erythrocytes and leucocytes, many of which are eosinophilic, large and small histiocytes, some of which contain inclusions of cell debris. All these cells are at times seen grouped together, one overlapping the other, with ill defined cell borders (Fig. 6). These groups are most difficult to identify correctly, especially if the nuclei of the histiocytes contain prominent nucleoli. They must then be carefully differentiated from malignant cells.

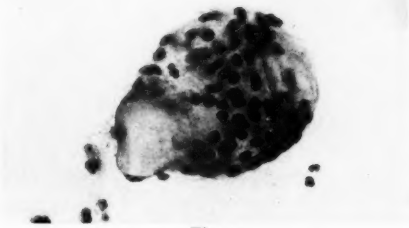

Fig. 7.

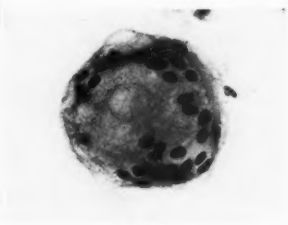

Fig. 8.

Fig. 7. Foreign body giant cell. ×320.
Fig. 8. Histiocytes in syncytial group with nuclei placed peripherally.

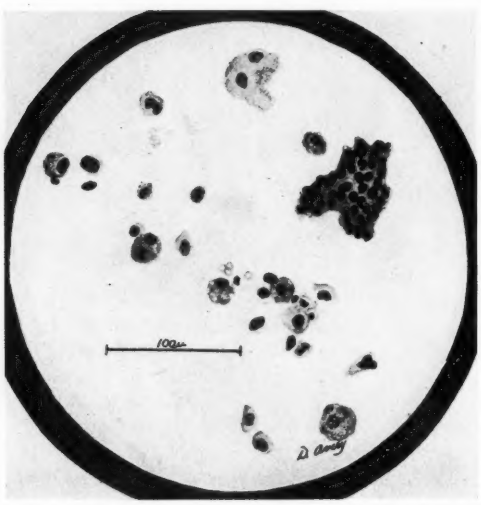

Fig. 9. Epithelial cells and histiocytes containing pigment found in material expressed from seminal vesicles. Camera lucida drawing. ×215.

Histiocytes often appear in syncytial groups as foreign body giant cells. They form large round or oval bodies in which cell membranes have disappeared (Fig. 7). The acidophilic cytoplasm in such a structure is abundant and is marked by faintly defined lines and vacuoles. The nuclei vary in number. If few, they are arranged peripherally, which gives

Fig. 11. Group of cancer cells. ×230.

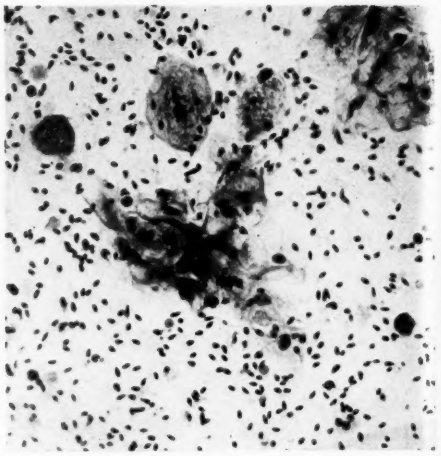

Fig. 10. Transitional cells, spermatozoa, histiocytes with dense masses of spermatozoa seen in "seminal vesicle smear."

the formation a very characteristic appearance (Fig. 8). The nuclei are usually distinct and fairly uniform in size. Occasionally, many nuclei are crowded into the syncytial formation and may be mistaken for groups of malignant cells. After experience is gained, however, they will readily be distinguished and identified.

SECRETION EXPRESSED FROM SEMINAL VESICLE

Quite frequently in the course of a prostatic massage, secretion is expressed which probably comes from the seminal vesicle or the ampulla of the ductus deferens, or both. This material contains cells which are not found in the prostatic secretion. Spermatozoa make up the largest part of the cell population. The epithelial cells in these smears are bizarre and may show marked variation and atypia. They appear in small sheets or more often singly. These cells made interpretation of smears at first uncertain until we were able to identify them as coming from the seminal vesicles. They were found in smears made by direct surface contact with seminal vesicles removed at surgery or autopsy, but were never found in contact smears prepared from prostates. Some of these epithelial cells contain granules of yellow pigment but in others

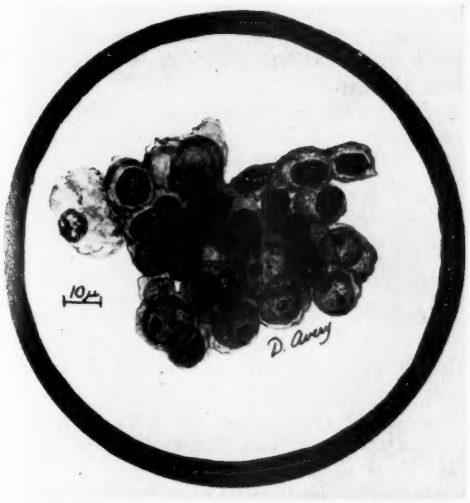

Fig. 12. Camera lucida drawing of group of cancer cells showing crowding of nuclei, anisonucleosis, hyperchromasia and large nucleoli. ×545.

this pigment is absent. Extracellular amorphous masses of pigment are frequently seen. The pigment can also be recognized in many histiocytes (Fig. 9), which have a finely vacuolized cytoplasm filled with pigment granules.

A most characteristic cell in the "seminal vesicle smear" is a histiocyte which engulfs spermatozoa (Fig. 10). It is a fairly large round cell about 25 micra in diameter with one or two eccentrically placed vesicular nuclei. Varying numbers of heads of spermatozoa can be ingested by these cells. If there are only a few the identity of the cell is unmistakable. However, the spermatozoa may form dense masses within these cells; they can then be confused with abnormal cells.

The liquid part of the secretion expressed from the seminal vesicles at times coagulates and is seen in the smear as large, homogeneous eosinophilic plaques. A high magnification survey of the cell elements in the "seminal vesicle smear" led to the discovery of very small cells (about 8 micra in diameter) which have a deep staining eosinophilic opaque cytoplasm. An eccentrically placed nucleus which stains very deeply gives the cell a characteristic appearance. Cells of the same size and staining qualities are found which

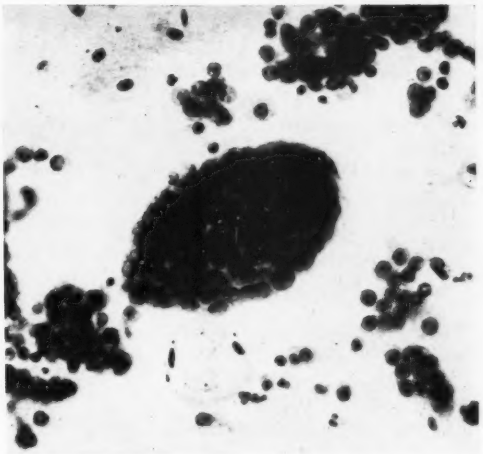

Fig. 13. Group of cancer cells showing little anisonucleosis. ×350.

contain two nuclei which are characteristically placed at opposite poles of the cells. Cells with three nuclei forming a trefoil are seen. Cells with more nuclei arranged peripherally are also found. These cells are spermatids which are formed in the seminiferous tubules and intermixed with the fully developed spermatozoa.

CANCER CELLS IN THE PROSTATIC SMEAR

Smears coming from patients who have carcinoma of the prostate are usually rich in cells.

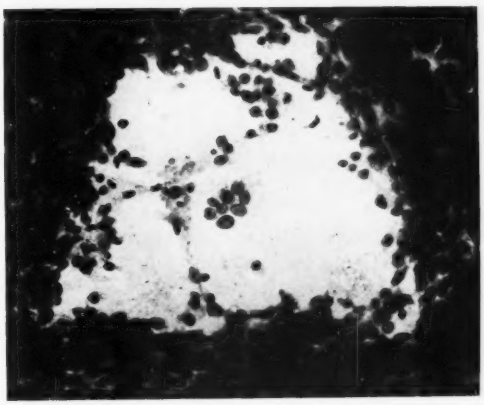

Fig. 14. Single cancer cells surrounded by pieces of tumor tissue. ×260.

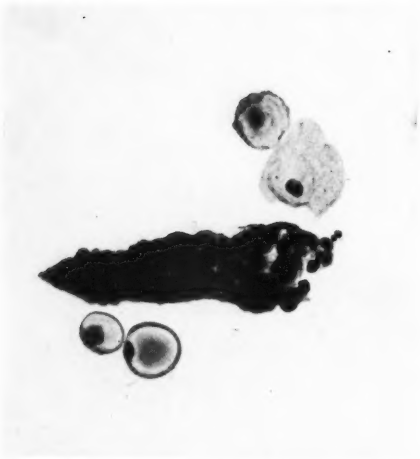

Fig. 15. Group of cancer cells in which nuclear detail is lost ("altered" malignant cells). Glycogenic cell. Smear from a patient with carcinoma of the prostate receiving estrogen medication. ×350.

It appears that cancer readily sheds cells into the secretion of this gland. The cancer cells can appear in large groups (Fig. 11). There is marked crowding of the nuclei which overlap one another or lie on top of each other. Cell membranes are not recognized, especially in the crowded parts of the group. Cytoplasm is scarce or displaced by the large nuclei. The size of the nuclei may vary greatly within the same group (Fig. 12). Some reach large proportions (12 micra); others remain rather small (6 micra). On the average, nuclei of malignant cells are larger (10 micra) than those of benign cells. The nuclear membrane is distinct and often thickened. The chromatin distribution is irregular with occasionally marked hyperchromasia. Single or multiple large (2 to 3.5 micra) nucleoli are characteristic.

One or more of these characteristics may be absent. Groups of cancer cells are found in which the size of the nuclei remains remarkably uniform (Fig. 13). However, marked crowding, scant cytoplasm, hyperchromasia, as well as large nucleoli characterize these groups as coming from a cancer. Cancer cells are also seen singly and in loosely arranged groups. Their detailed structure can then be accurately studied (Fig. 14). Small pieces of tumor tissue at times are sloughed off and found in the smear. Other cells will be seen intermingled with the cancer cells: columnar cells, cells from the transitional epithelium, histiocytes, leucocytes, erythrocytes and others, will be found in varying numbers depending upon the admixture of secretion in the specimen from parts of the prostate other than that harboring the cancer.

CELL CHANGES AFTER ESTROGEN THERAPY

Hormonal therapy produces marked changes in the cell population of the prostatic smear. This is understandable in view of the histiologic changes occurring in the genitourinary tract during estrogen medication. A profuse desquamation of the benign cells is noted in the smear. Large squamous cells (about 45 micra) with small pyknotic nuclei (4 micra) are shed in great numbers. They can become the most prominent members of the greatly increased cell population. This cell is easily recognized; it looks similar to the large superficial squamous cell characteristically seen in the vaginal smear. Some of these squamous cells contain glycogen, which is irregularly distributed throughout the cytoplasm. In addition to these cells which are probably desquamated from the epithelium of the urethra, cells appear in the smear which come from the prostate itself. They are round (about 28 micra) or oval cells (about 27 by 23 micra) with often peripherally placed nuclei (8 by 4 micra). The small cytoplasmatic rim encloses the dense glycogen containing center ("glycogenic cell") (Fig. 15). These cells are desquamated from areas of metaplasia which are formed in the prostate after estrogen stimulation (11).

The malignant cells shed after estrogen medication also undergo changes. The characteristics of the cancer cells become indistinct and the nuclei stain poorly. It is at times only possible by following these changes in serial smears to identify them as degenerated malignant cells ("altered" malignant cells). The number of malignant cells and cell groups usually decreases and if the prostatic cancer is sensitive to the estrogen they may disappear altogether. It is not unusual to search in vain for malig-

TABLE I.—CLINICAL AND CYTOLOGICAL FINDINGS

Histologic or clinical diagnosis	No. of cases	Prostatic smear		
		Positive	Negative	Suspicious
Carcinoma	100	88	5	7

nant cells in a smear from a patient who has been taking estrogen medication for months or years. Only large squamous cells from the urethra and "glycogenic" cells shed by the prostate will then be found.

RESULTS

The material investigated in this study was obtained from 616 different patients seen in the Division of Urology at the University of Rochester School of Medicine. Among those were 100 patients who had carcinoma of the prostate. On 46 patients the carcinoma was confirmed by histologic section. Fifty-four patients were judged clinically to have the disease; most of these had evidence of extension of the cancer, x-ray surveys showing metastasis or elevated phosphatase values. The examination of the prostatic smear of the 100 patients with carcinoma revealed malignant cells to be present in 88 cases (Table I). Seven smears were suspicious for cancer and in 5 cases no malignant cells could be found (false negative smears). Two patients whose smears failed to show malignant cells in their secretions had been on estrogen medication for several years. Both had responded well to the hormone treatment. It is therefore not surprising that no malignant cells were desquamated into the secretion in these 2 cases. Malignant cells were reported to be present in 2 patients who on histologic section proved to have benign prostatic hypertrophy (false positive smear). Among the 100 patients who later proved to have carcinoma were 5 not suspected of having the disease when first examined. The finding of cancer cells in their smears led to the correct diagnosis earlier than would have otherwise been possible. In these cases the cytologic investigation was of immeasurable help to the clinician and patient.

DISCUSSION

The results of this survey show that cancer of the prostate desquamates cells sufficiently characteristic to be recognized microscopically. They are found in a large percentage of patients harboring a cancer. A failure to find cancer cells in the smear does not exclude the presence of a malignant tumor. An adequately performed prostatic massage is essential for this study. The material obtained by massage must come from the prostate or no satisfactory interpretation can be given. In some instances a very hard prostate will fail to yield secretion on massage. In such a case no material will be available for cytologic interpretation. On occasion the gland may prove too tender to make adequate massage tolerable; a specimen containing only a few cells will then be prepared which is unsatisfactory for cytologic examination. If these mechanical obstacles are overcome or taken into consideration, the "false negative" report will become rare. Close co-operation between the clinician and the cytologist is most desirable and profitable. Even a negative smear can then become of significance. Negative physical finding and repeated failure to find malignant cells in several adequate specimens can be of clinical significance.

In our experience it has been possible to detect carcinoma of the prostate by smear before signs have become marked enough to make the clinical diagnosis certain. However, the question of how many prostatic cancers can be detected by prostatic smear in healthy men has not yet been investigated.

The reliability of the cytologic interpretation increases with the growth of the experience of the interpreter. A thorough familiarity with cells desquamated normally by the prostate, seminal vesicles, ampullae, and even testes is essential to be able to recognize the variations in health and disease.

SUMMARY

Cells found in the prostatic smear obtained by direct massage from patients with and without cancer of the prostate have been described. Eighty-eight secretions of 100 patients who had carcinoma showed malignant cells in the smear. The cytologic examination of the prostatic smear is found to be of great clinical value especially as an additional aid in cancer diagnosis.

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THE PROBLEM OF CALYCEAL DIVERTICULUM

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WHILE the calyceal diverticulum is a specific pathologic entity having significant clinical importance, all urologists are in agreement that little is known of this condition. However, most authors are at variance concerning the exact meaning of this term and as a result, it is often designated as pyelogenic cyst or hydrocalycosis. The paucity of the literature on this subject gives one the impression that this is a rare condition. The fact that calyceal diverticulum is not more frequently mentioned does not mean that it is not recognized. There is no doubt that such cases have been encountered but apparently otherwise classified. When a urologist encounters such a case, he is confronted with the problem of accurate diagnosis. As Prather points out, the urologist must answer the following questions: Is this a type of cyst or is it a dilated subdivision or diverticulum of a minor calyx? Should such a finding be treated surgically? We believe it should if certain criteria are fulfilled which will be enumerated in our summary.

Apparently, the same problem of terminology presented itself to Par P. Rayer in 1841 in his evaluation of a condition which he termed "kystes urinaires" in his volume *Traité des malades des reins*. His detailed and lucid description of a localized dilatation of a calyx is described in the chapter on hydronephrosis rather than those dealing with renal cyst. Fenger in 1873 and Brin in 1911 suggested the term "partial hydronephrosis." Damm in 1932 utilized the title of pyelogenic cyst to describe a solitary cyst of the kidney which demonstrated a small connecting channel with the renal pelvis. Quinby and Bright in 1935 maintained the designation "pyelogenic cyst" in their presentation. In 1935, O'Conor reported 2 cases of pyelogenic cyst but it is noted that these cavities were not outlined by pyelographic media in either case. Kohler in 1933 and Watkins and Winsbury-White in 1939 reviewed cases which fulfilled the criteria similar to the cases which are presented in this report. These authors reported their findings under the title of hydrocalycosis

Marked impetus to the study of this problem was given by Prather's presentation in 1941. This author described 3 cases which he termed as calyceal diverticulum. He differentiated the clinical and pathological findings noted in the cases of the calyceal diverticula and a solitary cyst of the kidney. Sterner and associates presented 3 cases. No surgical or histological confirmation was presented with this group of cases.

The term "calyceal diverticulum" is utilized to describe a cavity containing urine arising peripherally or distal to the calyx to which it is connected by a narrowed isthmus. As a rule, the involved calyx presents little or no evidence of obstructive renal uropathy, and the epithelial lining continues to that of the calyx. The lining of the diverticulum consisted of transitional epithelium demonstrating the same histologic characteristics as that of the renal pelvis or calyx (Figs. 1b, 3c).

In contradistinction to the above findings, a solitary cyst of the kidney demonstrates no communication with the renal pelvis or calyx and shows a flattened cuboidal lining epithelium which differs from that of renal pelvis or calyces. Calcifications of varying size may be found in calyceal diverticula. On the other hand, the term "hydrocalyx" is utilized to define the dilatation of a renal calyx arising because of obstruction existing in the infundibulum of the involved calyx. A calyceal diverticulum on the other hand containing urine is situated peripheral or distal to the calyx and is not a dilated major calyx or hydrocalyx. Radiologists have been prone to confuse para-

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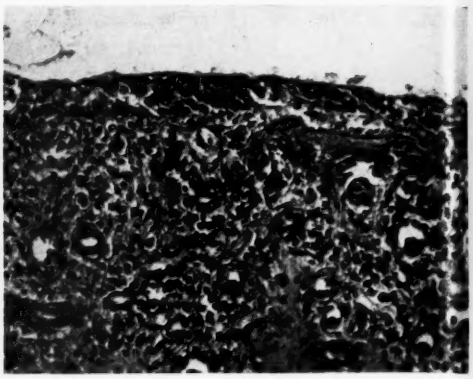

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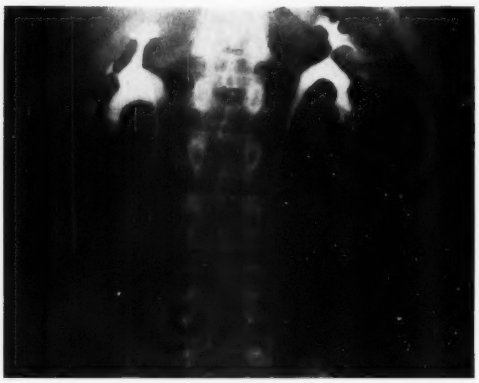
Fig. 1. a, Patient E.D.M. The sharply defined rounded area contained in the upper pole is demonstrated following intravenous and retrograde pyelographic studies in a 53 year old white male studied for hypertension. At operation, a left nephrectomy was done. The dye-filled area was first thought to represent a large dilated hydrocalyx caused by localized obliterating pyelonephritis. A review of the pathological material following operation demonstrated an intact calyx with a calyceal diverticulum. b, × 100. Section through the wall of the calyceal diverticulum. The epithelial lining consisted of several layers of transitional epithelial cells. This was supported by a thickened, fibrous stroma which shows infiltration with lymphocytes. The remaining portion of the kidney demonstrates evidences of chronic pyelonephritis. This section was obtained from the calyceal diverticulum found in the nephrectomized kidney following the operative procedure in April 1946. This patient died in 1950 of a cerebral vascular accident. His blood pressure which was 212/118 at the time of operation showed a persistent and marked drop following the operative procedure. In 1950, the return of the elevated blood pressure with significant eye ground changes recurred.

pelvic cysts with calyceal cysts. The parapelvic cysts lie in the renal substance adjacent to the pelvis. When enlarged and distorted by infection, they tend to rupture into the pelvis or calyx. The cavity formed by these ruptured cysts may be confused with calyceal diverticula. Adequate differentiation between them can be made by histologic studies of epithelial lining.



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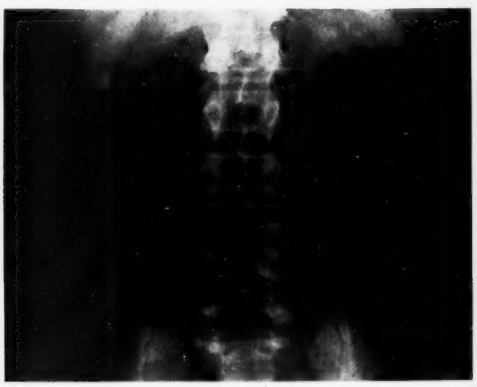

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Fig. 2. a, Patient C.H. The rounded area of increased density showing the connecting channel extending into the region of the superior segment of the inferior minor calyces is demonstrated by means of retrograde and pyelographic studies. At exploration, the surface of this kidney demonstrated no gross deformity and for this reason, no attempt to resect the inferior pole was made. This patient has been followed by serial graphic studies. b, Retention of dye in the calyceal diverticulum following the withdrawal of the ureteral catheter is demonstrated

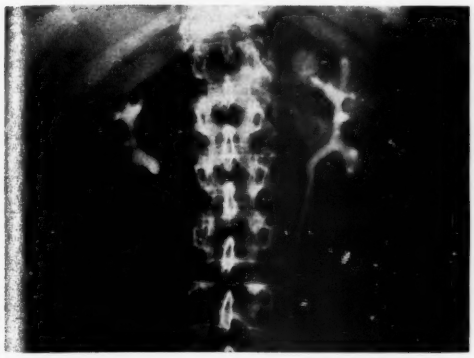

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Fig. 3. a, Patient D.A. Retrograde pyelographic studies demonstrating the large calyceal diverticulum contained in the mesial aspect of the superior pole of the right kidney. The calyceal diverticulum was demonstrated following intravenous and retrograde pyelographic studies. b, Intravenous pyelographic studies demonstrate filling of the calyceal diverticulum following the introduction of intravenous urographic dye. The peripheral margins are sharply defined. Note the well formed calyx contained beneath the inferior margins of the calyceal diverticulum. The connecting channel draining the diverticulum into the calyceal diverticulum is not demonstrated. c, Section made through the portion of the calyceal diverticulum. This section demonstrates the microscopic appearance of the wall of the calyceal diverticulum removed surgically. The pyelographic studies are demonstrated in a and b. Note the transitional epithelium which lines the diverticulum. This is in definite contrast to the single layer of flattened cuboidal cells which is characteristically found in the wall of a solitary cyst of the kidney.

Several factors have been proposed in an attempt to explain the mechanisms of the development of a calyceal diverticulum. Watkins has stressed the fact in his cases that the renal pelvis showed no evidence of obstruction. For this reason, the author postulated that some disorder in the function of the musculature at the neck of the calyx was present. This, in turn, would produce dilatation resulting from the achalasia or persistent spasm at the neck of a minor calyx.

Henle (4) utilizing his own as well as the anatomical findings of Disse, Haebler, and Muschat (4) proposed a different theory. Henle (4) suggested that the ring muscles surrounding the papilla and the musculature which is situated at the entrance to the calyx and the renal pelvis are capable of: (1) compressing the papilla, (2) shutting off the calyx from the pelvis. With such phenomena in play, dilatation of the segment of the upper urinary tract distal to this area of achalasia will result. It is possible that some of these mechanisms described to produce hydrocalycosis may also play some part in the formation of calyceal diverticula.

Other authors have contended that calyceal diverticula are of congenital origin. Hyams and Kenyon have suggested that it is possible for an obliterated pyelonephritis to involve a section of the calyx so as to produce scarring with the subsequent formation of a cyst distal to the area of scarring.

These authors point out that the lesions resulting from obliterative infundibular changes may resemble clinical and roentgenographic findings associated with calyceal diverticulum.

There is no specific clinical picture associated with calyceal diverticulum. An uncomplicated case of renal calyceal diverticu-

lum may show no clinical symptoms. The predominence of cases have been noted in males. Usually, such patients present themselves because of pain in the flank. Physical examination is usually negative. No gross mass could be palpated. The renal function of a kidney in which a calyceal diverticulum is present is good unless there is other associated diffuse renal disease. Should there be an associated pyelonephritis, the function of the kidney may be lowered. The renal function in such cases can be determined by the use of indigo carmine, phenolsulfonphthalein, and intravenous urography. Laboratory studies in such cases have usually been within normal limits. The nonprotein nitrogen is not elevated. The bacteriologic cultures as a rule demonstrate no growth. As a result of stasis of urine in the diverticulum, calculi are often formed. In the 2 cases in which calculi were present, no significant urinary tract infection could be demonstrated.

Intravenous urographic and retrograde pyelographic studies were utilized in all of the cases. It is important to note that suspected calyceal diverticula should be determined by both of these techniques. Anteroposterior, lateral, and oblique studies are distinctly necessary in order to localize the diverticular dilatation to demonstrate whether this is situated on the anterior or posterior aspect of the kidney. The roentgen studies demonstrated well defined opaque rounded areas lying adjacent and distal to the calyces filled with dye. The density of the dye in the diverticulum is similar to that demonstrated in the calyces. The diverticulum itself appears as a sharply delineated rounded area with well defined regular margins. Nonopaque calculi or detritus may produce a defect of the dye-filled shadow but no irregularities of the borders have been noted in our cases. The connecting channel draining the diverticulum empties into the calyx, and can often be defined roentgenographically. A characteristic finding is the retention of the dye in the diverticulum following the withdrawal of the ureteral catheters. The adjacent calyx may show the effects of extrinsic pressure upon its margin and in some cases, the flattening and spreading of the calyceal margins may be shown. In no case is there any evidence of obliteration of the calyceal margins. The sharp definition of the margins of the diverticulum and the absence of irregularity involving the diverticular walls or the adjoining margins of the calyx are characteristic roentgen findings. A rim of the cortical tissue on the peripheral aspect of the diverticulum is found in each of the cases. Laminographic studies made during the visualization of such a dye-filled cavity may also aid in its evaluation as well as its location.

The materials for this presentation are from the Departments of Radiology and Urology of The Grace Unit of the Grace-New Haven Community Hospital. The material was collected from the period 1946 until the present time. Of the cases reviewed, only 6 have been classed "calyceal diverticulum." In each of these 6 cases, the clinical histories were carefully reviewed and the age and duration of the symptoms were noted as well as the postoperative course of the patient in the group which subsequently came to exploration. Four of the 6 patients had been operated upon. Blocks of tissue were removed from various portions of the diverticular wall and slides were made. Histologic studies were then made from these specimens. Two of the 6 patients with calyceal diverticulum were women. The ages of the patients varied from 40 to 70 years. Three of the patients fell into the fourth decade, 2 in the fifth, and 1 in the seventh decade. One case was seen in 1946, 2 cases in 1948, 1 case in 1949, and 2 cases in 1950.

It is interesting to note that in 1 case, the calyceal diverticulum was found as an incidental study during the patient's hospital stay while she was being reviewed in an attempt to exclude the possibility of a malignant lesion. Five of the patients sought medical care because of abdominal and renal pain. The duration of the symptoms varied from 3 weeks to 15 years. In most cases, the physical findings were limited to moderate tenderness in the flank. No palpable masses in the kidney area could be palpated in any of the cases. Exploration was utilized in 4 of the 6 cases. In 1 case, a total nephrectomy was done because of the associated renal pathological lesions. In another case, a

calyceal diverticulum was described in the lower pole of the kidney in the intravenous and retrograde pyelographic studies. At the surgical exploration, the urologist palpated nothing of note and did not explore the parenchyma of the kidney. For this reason, no attempt to excise the cystic mass or explore the lower pole was made. The subsequent roentgen studies demonstrated the persistence of the calyceal diverticulum. Histologic specimens from the 3 patients demonstrated calyceal diverticula in which the epithelial lining of the cyst is similar to that demonstrated in the region of the kidney pelvis and calyx. In 2 of the cases, there were associated findings demonstrated in the kidney due to chronic pyelonephritis. In 1 of the cases, the calyceal diverticulum was demonstrated in the region of the lower pole; the remainder of the group demonstrated the calyceal diverticula in the upper pole. The postoperative course of the 4 patients was uneventful and the patients returned home. In the 1 case in which a total nephrectomy was done, the patient died 3½ years following the operative procedure because of cerebral vascular accident.

The management of a calyceal diverticulum is governed by its size, its location, and whether or not there are other associated renal pathological changes. Thus, a small calyceal diverticulum producing little or no symptomatology noted as an incidental finding following roentgenographic studies may be evaluated by subsequent serial studies. In such cases in which no further progression of the lesion is noted, surgical intervention may not be required. In cases in which surgery is deemed necessary, the goal sought for should be directed to: (1) the total eradication of the diverticular cavity, and (2) the enlargement of the channel draining the diverticulum into the corresponding calyx and renal pelvis.

The surgical procedures carried out by others as well as by ourselves consisted of the following: (1) Heminephrectomy if the diverticulum is large with an associated area of disease in the kidney which can be excised completely. The edge of the remaining healthy kidney is then closed primarily without drainage by means of Jianu-Deming type of sutures. (2) Diverticulectomy, complete localized resection of the involved area by a wedge-type resection. The edges of the kidney are again closed with Jianu-Deming type of sutures without drainage. (3) A nephrotomy incision is made in cases in which the diverticulum produces no visual deformity of the kidney contour, following evaluation of the roentgen studies and localization of the diverticulum. The diverticulum is located in the parenchyma, the channel connecting the diverticulum with the calyx is dilated. The nephrostomy tube is then placed into the renal pelvis traversing the calyx, its channel, and the diverticulum. The nephrotomy opening is closed around the catheter by the same type of sutures as used previously. The tube is removed 10 days after surgery but prior to removal of the tube, pyelographic studies are completed by injecting the contrast media through the nephrostomy tube to ascertain the patency of the ureter and to visualize its course.

SUMMARY

A review of the literature and an evaluation of the various theories proposed for the etiology of calyceal diverticulum have been presented. The confusion concerning the proper terminology to describe a connecting cavity arising distal to a calyx is emphasized. The clinical laboratory and roentgenographic features of such diverticula were evaluated. A group of 6 cases was presented and the roentgen and surgical findings in 4 of the patients operated upon were summarized. The surgical procedures utilized in such cases were discussed. The problem of evaluating a dye-filled cavity arising in relationship and distal to a calyx in the upper urinary tract is not an academic one. There are no characteristic symptoms. The diagnosis although established by roentgenographic means must be proved at operation and subsequent histologic studies

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AORTOGRAPHY: ITS INTERPRETATION AND VALUE

A Report of 200 Cases

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A QUARTER of a century has almost passed since the pioneering work of Dos Santos (1, 2) on aortography and still there remains a controversy as to the values versus the dangers of this procedure. Many consider aortography a useful and safe method of investigation in selected cases which present diagnostic and therapeutic problems; some—fearing the needle puncture of the aorta—are unwilling to adopt this approach. Those who criticize aortography claim that the information obtained does not warrant the risks involved in this procedure.

During the past 2 years we have seen 2,000 patients with peripheral vascular disease. Of this number, 190, or 9 per cent, have had aortography done during the course of their investigation. In addition to these, 10 aortographies were done for conditions other than peripheral vascular disease.

Was aortography necessary? Did it help in establishing the diagnosis? Did the information obtained influence the mode of treatment? What were the risks to the patient? These are some of the questions we propose to analyze in the following pages.

By definition, aortography is a roentgenographic examination of the aorta after the injection of an opaque media. It should be noted that in practice this procedure is more often done for the visualization of the main branches of the aorta than of the aorta itself. Therefore, the term is used freely and embraces a greater field than the definition implies.

Aortography should not be considered a routine practice in the medical investigation of patients with peripheral vascular disease. It is employed only after simpler methods have not disclosed the information necessary for the best management of the patient.

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INDICATIONS

In the group of 200 patients presented in this article aortography was indicated:

In patients with peripheral vascular disease in whom, because of therapy or prognosis, we needed to know the exact location and extent of the lesion. (1) Obliterative arteritis in which the femoral pulse is absent. For purposes of discussion and description, we divide this group into four types: thromboangiitis obliterans; arteriosclerosis obliterans or endarteritis senilis; endarteritis of the fifth decade or the mixed type; endarteritis of the aortic bifurcation with complete obliteration. (2) Aneurysms or arteriovenous fistulas. (3) Embolism of the aorta or its main branches. (4) Patients who are undergoing rectal surgery and who are known to have obstructive peripheral vascular disease. Aortography is done to obtain a clear assessment of the condition of the pelvic vessels because of the danger of interfering with the vital collateral circulation to the lower extremity.

In patients without known peripheral vascular disease in whom other types of investigation did not reveal the desired information. (1) Patients with abdominal masses, suspected renal or suprarenal tumors. (2) Women with suspected placenta previa.

Following is a tabulation of our series of aortographies according to indications:

Obliterative arteritis:		
Thromboangiitis obliterans	56	
Arteriosclerosis obliterans	83	
Mixed arteritis	22	
Endarteritis of the aortic bifurcation	14	
		175
Aneurysms and arteriovenous fistulas		8
Embolisms		2
Traumatic lesions of pelvic vessels		2
Suprarenal tumors		4
Placenta previa		4
Miscellaneous		5
Total		200

Fig. 1. Thromboangiitis obliterans.

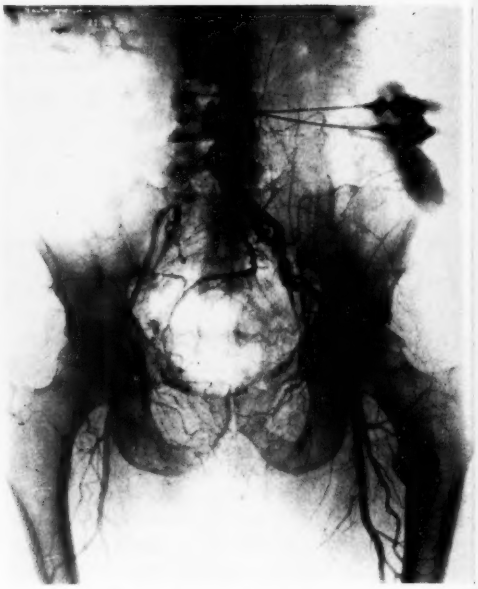

Fig. 2. Arteriosclerosis obliterans.

CONTRAINDICATIONS

There are few contraindications to performing aortography, but when any of the following are present they must be strictly observed: (1) Poor renal function. The dye is mainly excreted through the kidneys. (2) Impending gangrene in patients in whom even a minor degree of vasospasm, such as may occur during aortography, will precipitate the onset of this complication. (3) Allergy to iodine. (4) The general physical condition of patients in whom any surgical procedure is contraindicated.

TECHNIQUE

It is not the purpose of this article to discuss the technique of aortography at any length (7, 8); only certain points of importance will be mentioned.

Aortography should not be considered a minor surgical procedure. The general condition of the patient must be carefully investigated and the bleeding, coagulation and prothrombin times should be checked. The patient should be tested for iodine sensitivity a few days prior to the procedure. In our use of diodrast, 60 cubic centimeters of 70 per cent, we have had 1 severe reaction with vomiting, temporary oliguria, and urticaria.

Our patients received, as premedication, morphine and atropine 30 minutes before operation. A general anesthetic (we used intravenous sodium pentothal) is preferable, whenever possible. Otherwise the patient experiences a brief wave of intense heat and dyspnea as the dye passes through the cardiorespiratory system. When a general anesthesia is contraindicated, however, a spinal or epidural or even a local, may be used satisfactorily.

It is preferable to use the Dos Santos apparatus rather than a manual syringe injection, primarily because it standardizes the procedure and secondly because extravasation of fluid is much more likely to occur during manual injection, when even the slightest movement may displace the needle from the aorta. To prevent the possibility of injecting air into the aorta, 20 cubic centimeters of physiologic saline is placed on top of the diodrast and by watching this level between

Fig. 3. Arteriosclerosis obliterans.

Fig. 4. Mixed arteritis.

the saline and the diodrast, air should never escape into the circulation.

The patient is placed face down on the x-ray table with one x-ray cassette placed beneath the abdomen and pelvis and a second cassette beneath the thighs. The first exposure is taken at the end of the injection and the second exposure 4 to 8 seconds after the first. This time interval depends on the state of the circulation and varies with each patient.

To obtain a better concentration of the injected dye, we used two needles 14 centimeters long. They are introduced into the aorta 3 centimeters apart in the vertical plane, at the level of the upper lumbar vertebrae; the skin is punctured approximately four fingers' breadth to the left of the midline; and the needles are introduced downward and medially. The needles are connected with the Dos Santos apparatus by a Y-tube, in which the operator has allowed the fluid to descend just prior to injection, thus avoiding the possibility of air embolism.

As soon as the x-ray films have been exposed, the needles are removed and the patient turned on his back. If further surgical intervention is anticipated, it is wise to wait a few days, whenever possible, to prevent the patient's exposure to repeated stress.

An alternative method to the direct needle puncture of the aorta is by use of a retrograde arterial catheter (3, 4, 5). This is done by introducing a radio-opaque catheter into the brachial artery when the visualization of the thoracic aorta is desired, or into the circumflex branch of the profunda or the femoral artery for visualization of the abdominal aorta. While the retrograde method is very useful in outlining a particular segment of the abdominal aorta and its branches (e.g. renal vessels), it should never be used in patients with obliterative peripheral vascular disease for the following reasons: The catheter is introduced into the artery through a 2 to 3 millimeter opening which is later closed with silk sutures. The incidence of thrombosis in this region is high in patients with pre-existing obstructive vascular disease. There also may be difficulties in passing a catheter through a vessel already narrowed by vasospasm or thrombus

Fig. 5. Endarteritis of the bifurcation of the aorta with complete obliteration.

and in the latter case the thrombus may be dislodged, producing an embolus.

Our series consisted primarily of patients with peripheral vascular disease and therefore the direct translumbar aortic puncture method was used in 194 cases. Retrograde arterial catheterization was performed for investigation of 4 cases of suspected extravascular pathology, and thoracic aortic puncture was done in 2 cases.

COMPLICATIONS

In the hands of a careful and experienced operator, aortography carries only a few complications. The discomfort to the patient is minimal and there should never be a mortality.

The iodine sensitivity test will prevent reactions to the drug employed. By checking the tubing and the apparatus, and by carefully watching the diodrast-saline level throughout the injection, there should be no danger of introducing air into the aorta.

The needle puncture of the aorta, in itself, carries no dangers, except in cases of aneurysms. Here the operator should try to inject the aorta above the aneurysm or use the retrograde catheter method.

One complication which we do see occasionally is the interstitial extravasation of the dye. This, while not dangerous, is extremely painful and the discomfort may last up to 24 hours. If this occurs, 100 cubic centimeters of saline with 1 to 2 per cent novocain should be immediately injected into the same region.

The presence of temporary hypertension following the aortic injection of diodrast, as described by Bazy and Reboul, has not been demonstrated in any of our patients. On the contrary, we have noted a slight transitory fall in blood pressure.

INTERPRETATION

The recent advances in roentgenography have been remarkable. Almost every part and organ of the human body may now be directly or indirectly visualized. Angiography has added another valuable method of investigating certain types of disease. The following are the main points we look for in reading these films: (1) the exact location and extent of the lesion or lesions; (2) the state of the arterial wall in general and the wall adjacent to the obstruction in particular; (3) the state of the collateral circulation and the refilling of the main trunk below the obliteration; (4) the relations of the arteries to the organs supplied by them and to their adjacent structures.

Thromboangiitis obliterans. This is a generalized vascular disease characterized, as a rule, by a small vascular wall lesion and an extensive thrombosis. The aortography shows an intact arterial wall and very few, if any, collaterals. The circulation of the main trunk is not re-established below the lesion and there is a generalized peripheral vasospasm. This is well illustrated in Figure 1. The patient was a 30 year old male with a history of a rapidly progressive intermittent claudication. The left femoral pulse was absent. The aortogram reveals smooth, intact arterial walls. On the right side the femoral artery gradually narrows down to the mid-thigh region, where it is no larger than a fine thread. On the left, the femoral artery is obliterated, without the re-establishment of the arterial flow below the

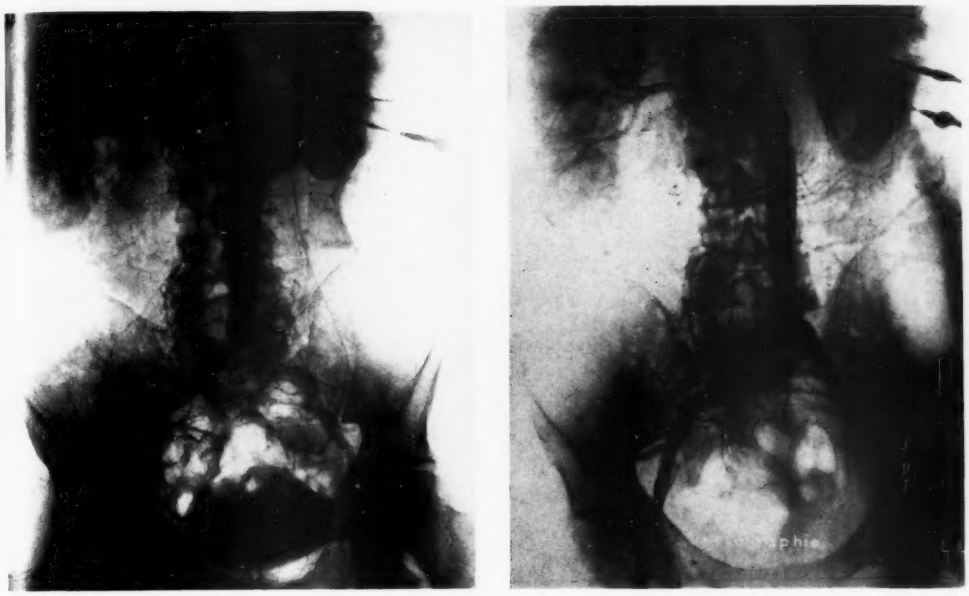

Fig. 6. a, left, Aneurysm of the abdominal aorta. b, Same patient 2 months postoperatively.

thrombus. This patient, in spite of bilateral lumbar sympathectomy, finally underwent a left mid-thigh amputation. Pathological examination of the femoral artery showed changes typical of thromboangiitis obliterans.

Arteriosclerosis obliterans. This group includes the atheromatous type with the lipoid deposits in the intima which may calcify, and the Monkeberg's sclerosis with the calcification of the media.

The x-ray findings on aortography in this group show the diameter of the vessels to be often increased and their course tortuous. Obliterations are numerous due to atheromatous changes and are often localized to one arterial trunk more than another. Collateral vessels are well developed and permit the blood to re-enter the main arterial trunk below the obliteration.

Figures 2 and 3 represent aortographies of patients, 65 and 70 years of age respectively, with advanced arteriosclerosis. The first shows a dilated aorta with an irregular outline and obliteration of the right common and internal iliac arteries. The external iliac and femoral arteries are patent, but the lumen of the latter is narrowed. The left iliofemoral system is well filled, but the arterial walls are altered by irregularities and strictures. Figure 3 shows a dilated, irregular aorta and the superior mesenteric, which is also dilated, can be seen running almost parallel with the aorta. The inferior mesenteric, on the other hand, is narrowed, probably due to atheromatous obstruction at its origin. On the right side there is marked stenosis of the common iliac just at the aortic bifurcation and the femoral is obliterated at the level of the lesser trochanter. A similar picture can be seen on the left and all the vessels are tortuous.

Mixed arteritis. This group could be described histologically as a segmental endarteritis obliterans with proliferation of the intima but without true atheromatous changes. The lesion is usually localized in the large arteries such as the external iliac or, on the other hand, in the distal arteries, often the tibialis posterior. In this latter group, the circulation to the leg is transmitted via the interosseus artery.

Fig. 7. Normal aortogram. Note the splenic, mesenteric and renal arteries. Also the outline of the kidneys.

TABLE I.—TYPES OF TREATMENT AFTER AORTOGRAPHY

Group	Thromboangiitis obliterans	Arteriosclerosis obliterans	Mixed arteritis	Endarteritis of bifurcation of aorta	Totals
No. of patients	56	83	22	14	175
Average age, years	44	63	48	38	
Sympathectomy, No. cases	33	44	5	14	96
Sympathectomy and arteriectomy, No. cases	12	18	7		37
Arteriectomy alone No. cases		12			12
Sympathectomy and suprarenalectomy No. cases	6				6
Sumpathectomy and graft, No. cases	2	1	5		8
Debouchage, No. cases			2		2
Amputation (primary treatment) No. cases		3			3
Medical	3	5	3		11

Figure 4 is the aortogram of a 50 year old man with severe intermittent claudication in the left calf and absent femoral pulsation on the left. The aortography revealed a well filled iliofemoral trunk on the right but with considerable stenosis of the external iliac at its origin. The arterial walls are smooth and normal in appearance. The left common iliac is obliterated and the external iliac and femoral are poorly filled, due to inadequate collateral circulation.

Endarteritis of the bifurcation of the aorta. This condition with complete obliteration was first described as a new syndrome in 1940 (6). It occurs in young men who present with difficulty in erection, extreme fatigability of the lower extremities (not true intermittent claudication), slow atrophy of the leg muscles, and moderate ischemia. Femoral pulses are absent on both sides. Bilateral lumbar ganglionectomy, with or without resection of the aortic bifurcation, gives good results.

The aortography (Fig. 5) is that of a 30 year old man who presented himself with the above mentioned symptoms and signs. Examination shows a complete obliteration of the terminal aorta with a collateral circulation on the right side. This patient had a bilateral sympathectomy 2 years ago and has been in normal health since.

Aneurysms and arteriovenous fistula. The diagnosis is usually made clinically and the value of aortography lies in the exact localization of the lesion. An example of this can be seen in Figure 6. The patient, a 35 year old male, had a slow growing, pulsating abdominal tumor. There was no history of trauma, no evidence of vascular disease elsewhere and the Wassermann reaction was negative. Because of the poor prognosis in this case, a resection of the aneurysm with aortic graft was suggested. After aortography had disclosed the site and extent of the aneurysm it was successfully resected by Doctor C. Dubost. The patient had an uneventful postoperative course and is now asymptomatic, but as only 2 months have passed since the operation, the final result cannot yet be evaluated.

As mentioned previously, we have included in our series 10 patients with *extravascular disease.* In these patients with renal neoplasms, suprarenal tumors, or placenta previa, investigation is made by comparing the blood supply of these organs to a normal film (Fig. 7).

Table I represents the types of treatment done after aortography on the 175 patients with obliterative peripheral vascular disease.

The 2 patients with Buerger's disease in whom grafts were done had each previously had a mid-thigh amputation of one extremity and subsequently developed obliteration of the external iliac artery of the remaining leg. In an effort to save this leg, arterial grafts were done, but they thrombosed and both patients died postoperatively. We feel that aortography is seldom indicated in patients with thromboangiitis obliterans and in the future we shall be more conservative in adopting this procedure in this group of patients. It does not give any indication as to prognosis and is of no help in determining the therapy, as reconstructive surgery in Buerger's disease has thus far proved unsuccessful.

Of the 83 patients with arteriosclerosis obliterans, 30, or 36.1 per cent, had arteriectomy and in 1 arterial grafting was carried out. Arteriectomy was performed mainly in those patients in whom aortography revealed marked stenosis of the artery without complete obliteration. The stenotic area was removed because, if allowed to remain, it would eventually obliterate and thrombus formation extending up the artery could occlude the orifices of the vital collateral vessels. These patients when followed-up have had much greater relief of pain than those in whom sympathectomy alone was done. The 1 patient of the arteriosclerosis obliterans group, in whom arterial grafting was done, had obliteration from the external iliac to the popliteal artery and the graft was 47 centimeters long. The graft is still patent 2 years postoperatively and the patient in good health.

In the mixed type of obliterative peripheral vascular disease, arterial grafts were performed in 5 of 22 patients (22.7 per cent); arteriectomy was done in 7 (31.8 per cent); and debouchage in 2 (0.9 per cent). Of the 5 patients in whom arterial grafting was done, 1 thrombosed; the remaining 4 are still patent 6 to 22 months postoperatively. All of the grafts were done by Dr. Jean Kunlin. In the 2 patients who had debouchage (incising the arterial wall, removing the obstruction, and closing the opening with interrupted silk sutures), the obstructions were in the common iliac and external iliac arteries. In both cases the vessels are still patent 18 months postoperatively. This procedure should not be undertaken if the obliterated area is more than 2 centimeters in length.

Fig. 8. Aortic obliteration, with good collateral circulation.

In endarteritis of the bifurcation of the aorta, aortography is of importance as a diagnostic procedure, as it is the only method of confirming the diagnosis. This is important, because this syndrome has a good prognosis, particularly following bilateral lumbar sympathectomy.

COMMENTS

The value of aortography as a diagnostic method of investigation is rather limited. It is confined to extravascular conditions such as renal, suprarenal tumors or other abdominal masses in which it is used as a supplement to other diagnostic procedures. In cases of traumatic or congenital pelvic aneurysms, a good x-ray film of the lesion will greatly facilitate the surgeon's task by localizing the pathologic condition. The same holds true for

arteriovenous fistulas. In emergency embolectomies, aortography is usually unnecessary, as a careful physical examination will reveal the location of the obstruction. In the 2 patients with traumatic lesions of the iliac vessels, whom we have seen, the site and extent of the injuries were well shown by aortography. Arterial grafts were done in both cases, in one successfully—the patient being still well 18 months postoperatively; in the second, an aneurysm developed at the point of suture 3 months postoperatively. This ruptured and the patient eventually came to amputation.

In obstructive peripheral vascular disease, the diagnosis is nearly always made clinically and here the only value of aortography is not as a diagnostic aid, but rather to give some indication as to treatment and prognosis. The knowledge of the exact location and extent of the lesion may be invaluable if reconstructive surgery is being considered. When grafting is to be done, it is important to know the length required and also the condition of the arterial wall. Suturing the arterial wall is a delicate procedure at any time and may be hazardous in the presence of poor diseased tissues.

Generally speaking, the higher the obliteration the better the prognosis. In slow occlusion of the terminal aorta or the common iliac artery, the collateral circulation is established in one of two ways: (1) by the lumbar arteries anastomosing with the branches of the external iliac; (2) by the inferior mesenteric, sigmoidal, and hemorrhoidal arteries anastomosing with branches of the internal iliac. The aortography in Figure 8 shows this well. The aorta is obliterated at the level of third lumbar vertebra. The inferior mesenteric and two large lumbar arteries just above the obliterated area form the main routes of anastomosis. The external iliac and femoral arteries are fairly well filled.

If the obliteration is in the external iliac, the prognosis is more grave, as the common iliac has no collateral branches. In this event, whenever possible, the obliteration should be surgically removed and a vascular graft done. In cases of femoral obliteration, it is the refilling of the popliteal artery below the obstruction which decides the future of the patient. The deep femoral artery is seldom involved and it is through this vessel that the collateral circulation to the popliteal develops. If the popliteal artery is not refilled, the patient will come to a mid-thigh amputation.

SUMMARY

A brief review of 200 aortographies, which we have done in the past 2 years, has been presented.

The interpretation of the x-ray films has been discussed, in particular in reference to peripheral vascular disease.

Aortography is a procedure which may be carried out without risk to the patient, but its practical applications and values are limited.

It is useful in a small group of patients with suspected abdominal or retroperitoneal tumors, in whom diagnosis is impossible to make by other simpler methods of investigation. In this group of patients, with relatively normal arterial walls, aortography is done by the retrograde catheter method.

In peripheral vascular disease, aortography should only be employed if resection or reconstructive surgery of the vascular lesion is to be considered. Here, the translumbar puncture of the aorta is the method of choice.

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THE ROENTGENOLOGY AND PATHOLOGY OF CYCLIC DISTURBANCES IN THE BREAST

With Special Reference to Their Surgical Diagnosis

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THE diagnosis of malignancy in the breast is obviously all important, but to this end a better understanding of benign disturbances must first be acquired. The detection of benign lesions by clinical and x-ray examination should make it possible to reduce *with safety* the large number of biopsies now performed for lack of adequate diagnostic methods. Radiology, which has been so valuable in other conditions, has failed to prove its worth in the diagnosis of breast lesions largely because of inadequate pathologic correlation. This we have endeavored to overcome.

In a series of 200 consecutive cases which came to operation at the Jewish Hospital, Philadelphia, radiologic and pathologic studies were made. These comprised lateral and tangential views of both breasts and serial sections of the entire specimen by the slicer method, as well as examination of frozen and paraffin sections. This bilateral approach afforded us an opportunity of correlating the pathological changes with the architectural details in the films; it was then possible to fit these joint findings with the clinical picture.

Accurate diagnosis of breast disease depends in great measure on accuracy of classification. To be of value such a classification must be applicable to clinical medicine, radiology, and pathology. It must be capable of being translated into microscopic terms, but it is not microscopic in its inception. It should have a clear clinical implication, not only of diagnosis, but also of prognosis and treatment. It should attempt to distinguish physiologic aberrations from the strictly pathologic. No system is entirely satisfactory, but so far as cyclic disturbances under the general heading of mammary dysplasia are concerned, we propose the following simple, logical, and easily applied classification.

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This work was partially supported by a grant from the American Cancer Society.

CLASSIFICATION OF BREAST LESIONS

1. Mazoplasia
   - Group I
   - Group II
2. Fibroadenoma
3. Secretory cystic disease
   - With or without plasma cell mastitis
4. Papilloma
5. Schimmelbusch disease (mastopathy)
6. Carcinoma

Before discussing the items classified above, it is well to clarify the anatomical and pathological terms employed. Such words as trabecula, stroma, parenchyma, and lobule are defined in books, but when applied to the breast, there is considerable difficulty in knowing just what is meant, a difficulty which most authors do not face squarely. The main confusion has arisen because of failure to grasp that the mammary parenchyma[1] is both epithelial and fibrous and that, unlikely as it may seem, both epithelial and fibrous elements arise from the same layer of undifferentiated basal cells. Since both parenchyma and stroma, i.e. ground substance, are fibrous, they are usually impossible to distinguish grossly. Moreover, when a lobule undergoes involution it is replaced by fibrous tissue and is then indistinguishable from the original stroma. Theoretically, it is still part of the parenchyma. A trabecula, defined as forming an essential part of the stroma, cannot in

[1]Parenchyma: The essential or functional elements of an organ as distinguished from its stroma or framework (Dorland).

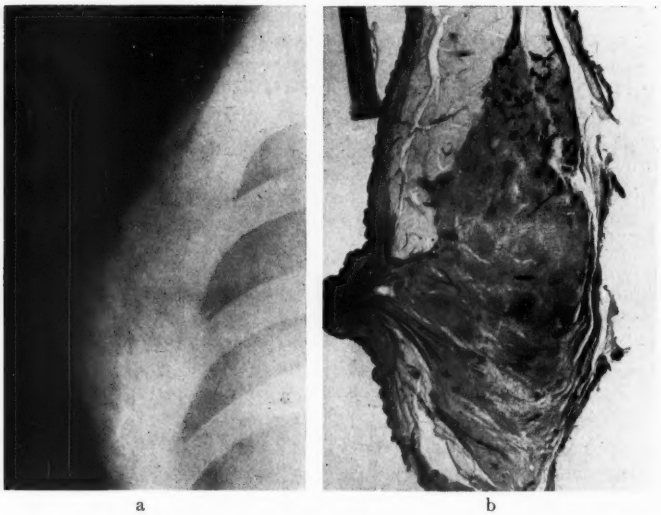

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Fig. 1. Mazoplasia, group I. Age 33 years. Last menstrual period 24 days before simple mastectomy. X-ray film shows uniform increased density of breast tissue and is characteristic of mazoplasia I. Slicer section through entire breast, natural size, shows marked increase in intraductal fibrous tissue and extreme paucity of lobules.

practice be separated from the parenchyma either grossly or radiologically. For lack of a better term, we are obliged to use trabecula to cover both stroma and parenchyma. "Lobule" also gives rise to some ambiguity. A lobule is a group of ductules arising from the distal extremity of a duct. It must not be confused with the club-shaped terminal ducts of the adolescent. In the adult, because of hormone imbalance, ducts may only reach the adolescent stage, instead of developing lobules. Or a lobule may begin to develop, but, instead of continued subdivision brought about by proliferation at certain growing points, the entire duct wall grows. This results in a collection of cysts, which are small or large depending on the stage of development reached before the abnormal stimulus intervened and also depending on its intensity. The variability of the process makes it difficult to decide at what point to use the term lobule for these structures.

MAZOPLASIA

Mazoplasia, Group I, occurred in 14 of our series of 200 patients who came to operation. The symptomatology has been thoroughly covered by Semb and by Cheatle and Cutler. For full details we refer the reader to their classical monographs. The average age in our series was 33 years 5 months. Duration of symptoms varied from 2 weeks to 4½ years. Pain, usually premenstrual and seldom severe, was present in 9 cases. Diffuse nodular areas or circumscribed masses were found in all at one time or another. In 3 patients the mass disappeared after menstruation to return during the premenstrual phase. While menstruation was regular in all but 3, marital histories were fairly characteristic of mammary dysplasia. Of 4 patients married for more than 5 years, none had children, although contraceptives were not used. Three were single; 2 were divorced after the birth of 1 child; 1 was a widow with 1 child; 1 desired no children. Of the 2 remaining patients, 1, aged 35 years, had 2 children and the other, aged 28 years in whom the lesion was extremely early, had 1 child. It is significant that 4 patients gave a history of operations on the same or opposite breast, 1 twice before; out

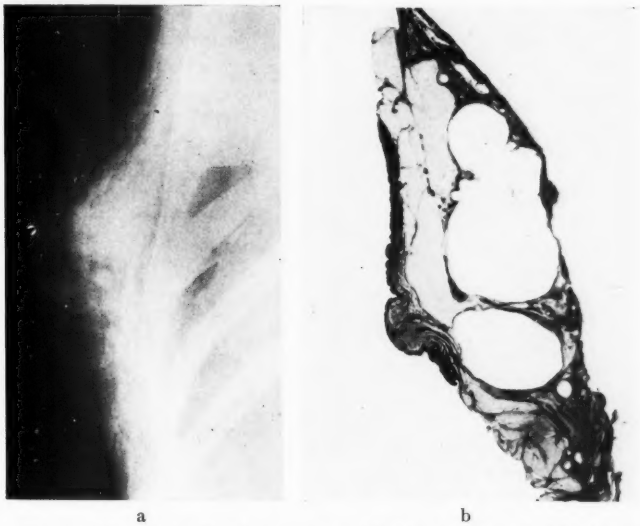

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Fig. 2. Mazoplasia II. Age 39 years. Sudden swelling of right breast following a 6 months' course of large doses of estrogen. X-ray film shows numbers of superimposed cysts. Their outlines can be seen where they impinge on the superficial fatty layer. The roentgenogram presents a more confused picture than the pathologic section because it is 3 dimensional and in the pathologic section only 2 dimensions are seen. Slicer section: small breast containing a cluster of large cysts impinging on the areola. Smaller cysts occur throughout the breast. Breast lobules are crowded together and are mostly poorly differentiated.

of 12 cases, 5 had previous pelvic operations (2 hysterectomies for myomas, 1 ovariectomy and myomectomy, 2 dilatation and curettage). Propaganda, swaying both patient and physician, was responsible for surgery in several cases. Since in this group the condition is mainly physiological, it should be obvious that surgery is not indicated. In the present state of our knowledge it is not always easy to prescribe the right remedy, but once the patient understands that she does not have cancer and that the breast is only reacting to some trouble elsewhere, she is not likely to clamor for surgery. Practically all the cases were diagnosed clinically as cystic disease and in some of them the tumors were certainly clinically indistinguishable from a tense cystic mass. The radiologic findings, however, would have made the diagnosis clear.

Pathologically in this group the changes may be general or focal. The breast tends to be small, hard, and nodular. Often no pathologic changes are seen on inspection. Occasionally the breast tissue will even feel normal. Microscopically, the outstanding feature of this group is hyperplasia of the fibrillary (intraductal) zone which lies immediately beneath the epithelium of the ducts. The duct presents a collar of fibrillary tissue many times the diameter of its lumen. This may cause compression atrophy of the epithelium with narrowing or complete obliteration of the lumen. In other ducts the epithelium proliferates to some extent and these ducts will show mild dilatation. There is considerable diminution in the number of lobules. In their place one finds groups of club-shaped dilated ducts as in the adolescent breast. If lobules are present they are poorly developed. The ductules are few. Their lumens are widely separated and they tend to be slightly dilated. The term "blunt duct adenosis" applied to these structures is a misnomer. Adenosis is sometimes present in mazoplasia, group II. In group I there

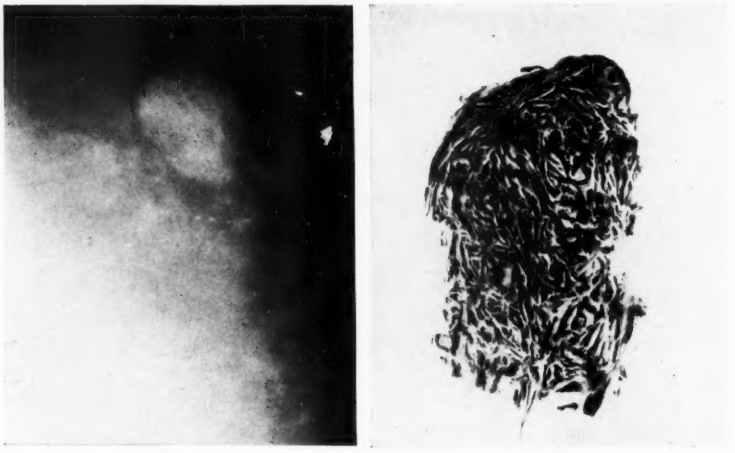

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Fig. 3. Fibroadenoma. Age 45 years. Roentgenogram shows an isolated tumor less dense than a cyst, smooth, but not symmetrical. Margins are lobulated and not as circular as would be expected in a cyst. Tumor 3.2 by 2.5 centimeters sent in fragments. Microscopic section shows fibroadenoma of the usual intracanalicular type.

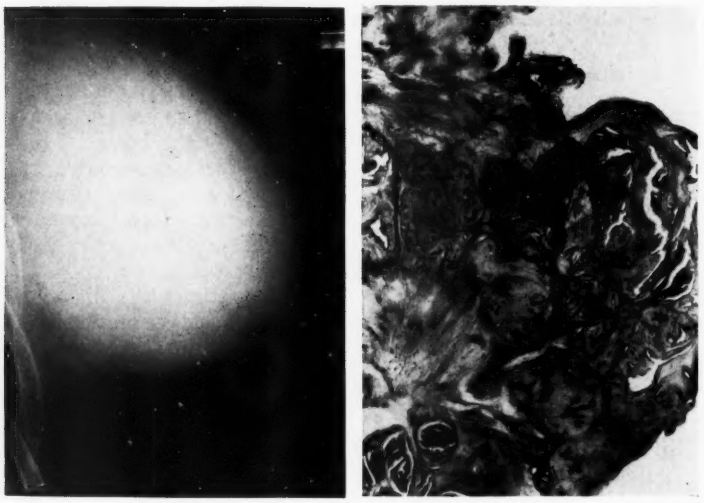

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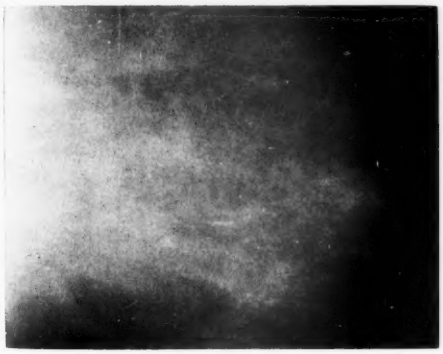
Fig. 4. Giant fibroadenoma. Age 45 years. Greater part of breast occupied by a hard mass, fixed to underlying tissue but not to skin. Roentgenogram shows a homogeneous mass which is not as sharply outlined as a cyst and not as dense. Moreover there are no loculi such as would be seen in a cystic mass. A solitary cyst seldom occupies so large an area. The mass cuts across the prepectoral line but its smoothness precludes malignancy. The tumor is a giant fibroadenoma formed by a conglomeration of nodules, varying greatly in their architecture. At one edge the tumor merges with the breast.

is lack of adult lobular development; there is less, not more, glandular tissue and the differentiation of ducts into ductules has not taken place. In slicer sections, these sparse thickened ducts stand out clearly under the dissecting microscope in contradistinction to normal lobules in which the individual ductules in the last half of the cycle are so close together that they are hard or even impossible to make out under the low magnification used. Focal intraductal hyperplasia when long continued leads to fibroadenoma of the intracanalicular type which often accompanies mazoplasia. Microscopic fibroadenomas are commonly present in these breasts. Most of them seem to disappear when the normal physiologic balance is restored.

The x-ray findings in this group are characterized by a uniformity and homogeneity of the tissue density in the breast. The breast appears healthy and resembles the normal breast of the adolescent or young adult, or that of early pregnancy. There is no accentuation of the subcutaneous extension of Cooper's ligament. The anterior surface of the breast tissue proper is sharply separated from the layer of overlying subcutaneous fat. The anterior contour of the glandular portion of the breast is smooth and lacks the bulges or lobulations which might be caused by isolated cysts or tumors.

Fig. 5. Secretory cystic disease. Focal plasma cell mastitis. Age 51 years. Serous discharge from left nipple 6 weeks; bloody discharge 1 month. Upper portion of breast is occupied by a nontrabeculated mass. The margins are smooth and bulge, suggesting cysts. This is associated with flame-like digitations of perifocal trabeculae as is characteristic of secretory cystic disease. The picture as a whole indicates plasma cell mastitis, especially since secondary signs of malignant disease are absent. Diagnosis confirmed by operation.



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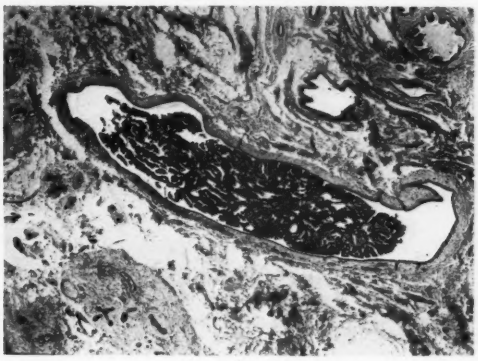

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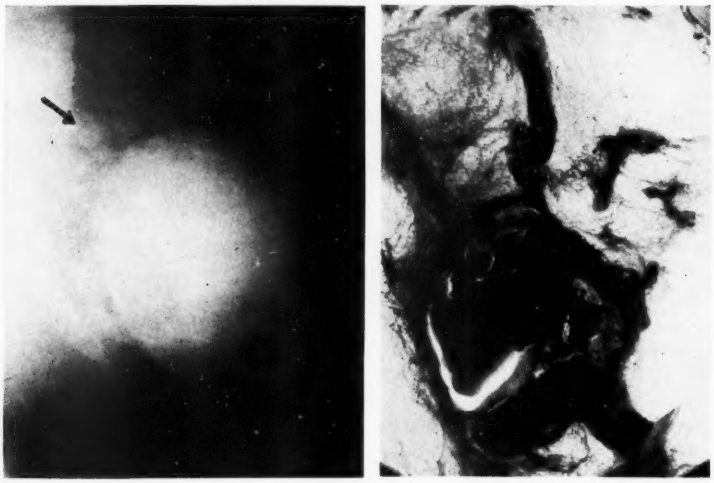
Fig. 6. Intraductal papillomas. Age 63 years. Serous discharge from right nipple 3 weeks. Papillomatous tissue found in discharge. Bloody discharge 2 months later. Roentgenogram shows dilated distorted ducts leading to the nipple. These ducts are beaded and corrugated, not flame-like as in secretory cystic disease. There are no secondary signs of malignancy with which these appearances might also be confused. Pathologic diagnosis: Multiple benign papillomas. Photomicrograph of one of these.



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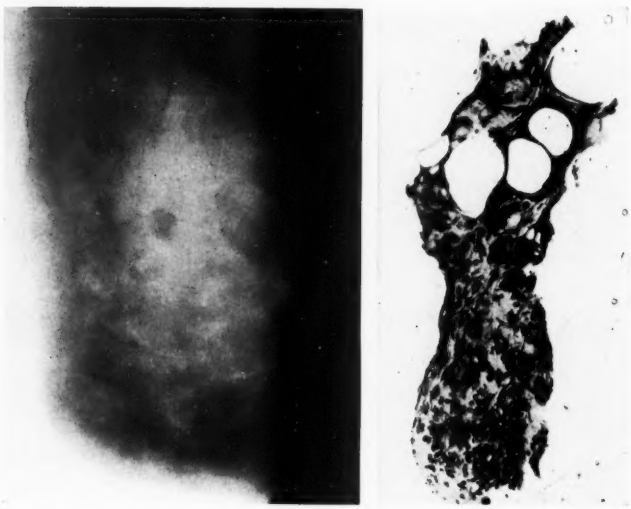

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Fig. 8.

Fig. 7. Intracystic papillomas. Age 68 years. Lump in left breast 4 years—painful at first, varies in size. Examination showed large mass above and below nipple. Roentgenogram presents an opaque, easily visible cyst with smaller cysts nearby. Breast tissue is mottled; narrow digitations with beading are seen. Simple mastectomy: cyst 4 by 5 centimeters filled with grumous brown material with pieces of necrotic papilloma floating in it. Other hemorrhagic cysts with papillomas also found, together with numbers of minute fibroadenomas. Illustration shows one of the smaller cysts containing papillomas and blood clot. (Indicated by arrow in x-ray film.)

Fig. 8. Schimmelbusch disease. Age 45 years. Gradual onset of breast symptoms 6 years but no mass found until 1 year ago. Now has multiple cysts. X-ray picture is an exaggeration of mazoplasia II which it resembles. There is much less uniformity in the changes than is seen in mazoplasia II. Breast tissue presents large and small cysts throughout. Some have inspissated contents, others are of the simple type. Intraductal proliferation and papillomatosis and intraductal and interlobular fibrosis also present.

When fat has invaded the glandular portion, the normal stromal architecture is not disturbed. The distribution of the fat is uniform, and the stromal strands, consisting of glandular and supporting tissues, make a symmetrical expanding pattern from the nipple to the base of the breast (Fig. 1).

The density of the breast in the film is a reflection of thickened trabeculae which, as the pathologist's section shows, are caused by intraductal fibrosis. The microscopic fibroadenomas are merely a continuation of this process and are of course not visible except as part of the general increased density; they are too small to be picked out as tumors. Even isolated fibroadenomas, 1 or more centimeters in diameter, are often not discernible in this type of breast, since they are of the same density as the surrounding mammary tissue.

Mazoplasia, group II, comprised 39 cases. The average age incidence was 40 years 8 months, i.e. 7 years later than in group I. The symptoms are similar, but the duration was generally longer, sometimes many years. Menstrual irregularities, as might be expected, were more frequent. Ten patients had a total of 15 breast operations performed previous to the present admission, 11 had had pelvic operations, including 4 hysterectomies, 3 others had known pelvic lesions, 3 had enlarged thyroids. "Nervousness" was very common. The marital histories were similar to those in the first group.

Pathologically, the prominent characteristic of mazoplasia, group II, in addition to intraductal fibrosis and microscopic fibroadenomas, is the presence of cysts. These are often so striking that the attention is focused on them to the exclusion of other fundamental features. The lining of the cysts is smooth; in the smaller cysts there are the usual two layers of epithelium, in the large cysts the lining is mostly flattened and atrophic. Besides cyst formation there is apt to be an increase in lobules, but the individual lobules are poorly differentiated. Like those in the first group the ductules are few and are often dilated. Between the cysts and the groups of lobules intraductal fibrosis, as described in mazoplasia, group I, is seen. The changes may be general or focal and intermediate forms are common. One or more sectors of the breast may be affected to the exclusion of the rest of the organ.

At first glance it might seem arbitrary to classify what has been called cystic disease under "mazoplasia." A different name might be found, but it is important to emphasize the close relationship between the two groups. There are fundamental reasons for linking them. The essential distinction is that in group II, epithelial cells multiply and more or less keep pace with the surrounding fibrillary tissue. When this happens the duct as a whole increases in length and diameter, the lumen dilates, and a cyst is formed. There is no papillomatosis, and although the cysts may reach very large dimensions their lining is smooth. This means that the condition is still quasiphysiological. These patients, like those of the first group, need not be operated upon unless their discomfort demands it; and this is a second and very practical reason for bringing them together.

The x-ray appearance of the breast is similar to that in group I, but, because of the pressure of cysts, other patterns supervene. Small cysts may not be recognizable in compact, dense breast tissue. Larger cysts, especially if fat is also present, become clearly delineated due to their sharp, smooth margins. The more fat in a breast, the easier the visualization of the cysts. Even in dense compact breasts, cysts reveal their presence by bulging displacement of the stroma, although here a certain skill and experience on the part of the radiologist is necessary for their discernment (Fig. 2).

FIBROADENOMA

Fibroadenoma was the presenting lesion in 37 cases. Fibroadenomas originate in circumscribed foci of mazoplasia. They arise as a rule from terminal branches of ducts. The stages from intraductal and occasionally epithelial hyperplasia to the formation of coalescing nodules and encapsulation can be clearly followed under the dissecting microscope. In the earliest stages a main duct can be seen entering the tumor or tumor

nodule. Later this duct becomes compressed and connection with the surrounding breast is lost. It may be that this loss of continuity is the "point of no return," in that regression of the mass is then unlikely to take place. Often only one side of the tumor is encapsulated. On the unencapsulated side, the mass is likely to receive additions from small mazoplastic nodules which lie next to it. The fibroadenomatous tissue continues to be influenced by the cyclic hormones which are producing changes in the rest of the breast, but probably owing to a lessened blood supply and to mechanical difficulties it does this only imperfectly (7).

Since the substance of a fibroadenoma is the same as that of a trabecula, the reason for its nonvisibility in the x-ray film is apparent. Under the age of 20 the breast is usually of the adolescent type, and this type of structure is the foundation of fibroadenoma. Therefore, in these patients, a clinically palpable tumor which is invisible by x-ray examination is apt to be a fibroadenoma. Obviously, the radiologist can only make this diagnosis when the history is known. The film is characteristic of mazoplasia I or of a normal adolescent breast.

With advancing age and increasing fat deposit in the breast the diagnosis becomes easier. When visible, a fibroadenoma has a smooth edge. It is less radio-opaque than a cyst and large fibroadenomas are not indented as a group of cysts would be (Fig. 3). Large fibroadenomas will push the surrounding trabeculae aside in the same manner as a cyst (Fig. 4) but small fibroadenomas are apt to merge with the surrounding parenchyma. Single fibroadenomas are not as symmetrical in outline as cysts. In older people especially, a fibroadenoma may undergo calcification and is then easily detected in the x-ray film. Some fibroadenomas cannot be distinguished from cysts, in spite of these aids to diagnosis.

SECRETORY CYSTIC DISEASE

Secretory cystic disease, like mazoplasia, is the result of hormone imbalance. Mazoplasia is the counterpart of persistent proliferative phase in the uterus; secretory disease corresponds to the secretory phase. Transitions between the simple cysts of mazoplasia and secretory cysts are common. The correct diagnosis of secretory disease and of its sequel, plasma cell mastitis, is of considerable importance since it is liable to be mistaken for carcinoma. In secretory cystic disease the epithelium differentiates and is destroyed, therefore carcinoma cannot supervene in the affected ducts. On the other hand, the accumulation and degeneration of products of secretion are the direct cause of plasma cell mastitis (15).

Secretory cystic disease was present in 16 cases. Two patients, aged 28 and 30 years respectively, were early cases showing secretion of milk in a nonpregnant breast. The first of these was not operated upon. Dilated ducts, reaching their maximum swelling just before menstruation, were palpable in both breasts. She was observed for several months. After treatment with testosterone the milky discharge ceased and the swellings subsided. In the second, the diagnosis was confirmed by operation.

The average age of the remaining 14 was 47 years. They presented dilated ducts and cysts filled with characteristic inspissated secretion. This varied from chalky, greyish or yellowish white, to brown, green, reddish or even frankly bloody. Worm-like casts exuded from the ducts on pressure, hence the term "comedomastitis" which, like "nutmeg" liver or "hardbake" spleen, is purely descriptive and has no place in serious classification. The disease is more often local than general. In 10 of 14 cases, the affected ducts were situated beneath the nipple. Bleeding or discharge from the nipple occurred in 6 of these. The history of pain and a tender mass is generally a short one—under 1 month in 12 cases. In contrast to the mazoplasias, the marital histories are normal; the majority nursed their children, but 4 had puerperal mastitis, and 1 stopped nursing because of an attack of influenza. Trauma was a direct antecedent in 2 cases. In 10 patients secretory cystic disease was accompanied by foci of plasma cell mastitis.

Pathologically, proliferation of the epithelial cells is followed by differentiation into

colostrum-like cells. These are shed into the ducts where they degenerate. Their numbers are increased by fat laden histiocytes which migrate into the ducts from the surrounding connective tissue. In long standing cases the duct epithelium is completely destroyed and replaced by a flattened membrane. The lobules between the affected ducts may be compressed and atrophied. Sooner or later the degenerated material in the ducts gives rise to an inflammatory reaction similar to that seen in traumatic fat necrosis, chronic lactation mastitis, and so-called infected galactocele. This is the plasma cell mastitis of Adair.

The x-ray film shows coarse digitations often flame-like in shape *which run in the line of the breast trabeculae*. Should plasma cell mastitis supervene a localized tumor appears surrounded by a zone of edema. The picture differs from mazoplasia II in that multiple small rounded cysts are normally absent and the trabeculae are more uniform. In mazoplasia II, edema, increased vascularity, and flame-like digitations are lacking. The tumor of plasma cell mastitis is distinguished from carcinoma by its edematous appearance and by its lack of the typical carcinoma margin. Carcinomatous extensions cut across the breast trabeculae while the "tumor" infiltrations of plasma cell mastitis run with them. Moreover, most of the secondary signs of carcinoma are absent (Fig. 5).

PAPILLOMA

Papilloma was diagnosed in 7 cases. Papillary tumors may be benign or malignant. We agree with Haagensen, Stout, and Phillips that the vast majority are benign and remain so. The absence of a palpable tumor excludes carcinoma, but the presence of a tumor is no indication of cancer. The conversion of a benign papilloma into a carcinoma is a rare event and may take a long time (20 years in 1 of our cases). It is much more common for papillomas to heal by fibrosis. The process can often be followed under the microscope. Some rapidly growing papillomas present a jumble of epithelial and myoepithelial cells. In their immature stage both present very large nuclei which could be confused with carcinoma. But the epithelial cells can be seen to be forming ducts and the myoepithelial cells are distinguished by long tails of cytoplasm containing fine fibrils. The myoepithelium becomes transformed into the fibrous cores of the papillae, and when myoepithelial proliferation is intense, the entire tumor becomes converted into fibrous tissue. Malignant papillomas do not show this intense myoepithelial hyperplasia. Since these criteria are merely microscopic, it is obvious that all papillomas need at least local excision.

Diagnosis of papilloma is most easily made in patients in whom a discharge from the nipple contains particles of the growth. However, x-ray examination is often of assistance and the radiologic diagnosis may be positive in the absence of other signs. It is convenient, especially from the x-ray point of view, to divide papillomas into intraductal, in which the tumor occupies a distended duct, and intracystic, in which the tumor springs from the wall of a fluid-containing cyst. Occasionally, the growth becomes infected and the cavity is filled with pus.

In the x-ray film of intraductal papilloma, the affected ducts are elongated and varicose. There may be some resemblance to secretory cystic disease but broad, finger-like trabeculations are usually not seen, and if present, are scanty. Secondary signs of carcinoma are absent (Fig. 6). Intracystic papilloma is most readily recognized by the remarkable ease with which the cyst can be seen. This is not due to the papilloma per se, but to the fact that most papillomas bleed. In addition to the growth, the cyst contains hemosiderin from disintegrated blood and necrotic debris, as well as fresh blood. The iron-containing hemosiderin, especially, is radio-opaque (Fig. 7).

SCHIMMELBUSCH DISEASE

Schimmelbusch disease, comprising 4 well developed cases in our series, is known under various names. Any one of them is to be preferred to "chronic cystic mastitis" which, as Foote and Stewart have said, is little bet-

ter than a conditioned reflex of the surgical mind. European authors, following Moszkowicz, tend to use the term mastopathy to designate this condition. Schimmelbusch himself, writing in 1892, claimed no priority and referred to Astley Cooper (1828) for a description of the first case. Reclus (1865) and Velpeau (1854) called attention to the cystic breast. To Benjamin Brodie (1840) we owe the first systematic description under the title of "Serocystic Disease of the Breast." Brodie's outlook is interestingly modern. He states that "it is needless to remove what appears to be a solitary cyst, as it is always highly probable that there are other cysts . . . or that such cysts will be formed afterwards if they do not exist already. Removal of the entire breast is unjustifiable" (unless these cysts are inconveniently bulky).

Schimmelbusch disease or mastopathy may best be defined as mazoplasia II with additional, frankly pathologic features, such as intraductal papillomas and myoepithelial hyperplasia ("epithelial spilling," sclerosing adenosis); the myoepithelial hyperplasia, as in papillomas, ends in fibrosis, sometimes followed by hyalinization and calcification of the tissue. The point is that in neither papilloma nor sclerosing adenosis does the breast tissue return to normal. In mazoplasia the breast does return to normal when the abnormal hormonal stimuli have ceased to operate, unless the distortion is very great. In mazoplasia, besides the cysts which are harmless from the clinical and prognostic point of view, there may be some multiplication of poorly differentiated lobules (adenosis). These may regress during menstruation, otherwise they furnish material for new cysts. But in Schimmelbusch disease, cell proliferation often proceeds more rapidly and although differentiation still takes place normally, organization cannot keep pace with the process and other patterns will appear. As long as cell differentiation occurs no matter how great the hyperplasia, there will be no malignancy. The danger zones are not the cysts nor the myoepithelial sclerosis nor even the papillomas, but hyperplasia of poorly differentiated lobules. This we can agree to call adenosis. The presence of cysts of the mazoplastic type is evidence of cell differentiation, but extensive adenosis unaccompanied by macroscopic cysts is exceedingly common in young women with carcinoma, and we agree with Foote and Stewart that this form of adenosis may well be precancerous. Unfortunately, there is no clear clinical sign by which it can be known.

The radiologic picture of Schimmelbusch disease closely resembles, and may be indistinguishable from, advanced cases of mazoplasia II. The changes are more marked than in mazoplasia II and there is greater distortion of the entire architectural pattern. The breast is crisscrossed by many secondary trabeculae. Beading and tortuosity of trabeculae can occasionally be made out (Fig. 8).

DISCUSSION

The newer conception of breast disease as embodied in our classification is based on the work begun in 1924 by Peyron (12, 13) and his colleagues and continued more recently by Kuzma and Biggs.

The essential underlying factor, which is common to physiological growth, mazoplasia, and mammary dysplasia in general, is hyperplasia of the undifferentiated cells of the basal layer in the ducts. Peyron in 1924 was the first to show that in mammary tumors of animals these cells of the basal layer give rise to both epithelial and myoepithelial cells. Masson, in his textbook published in 1923, describes and figures myoepithelial hyperplasia in Schimmelbusch disease, but does not trace the origin and evolution of the cells. Peyron's work was repeated in 1926, and he and his colleagues demonstrated the conversion of the myoepithelium into fibrillary intraductal tissue. Kuzma showed that the cells of so-called epithelial spilling were in reality myoepithelial cells. Rosemary Biggs portrayed the origin of the myoepithelial cells and their transition to intraductal fibrous tissue in a variety of conditions. The transition from epithelium to myoepithelium is clearly seen in many of our preparations, and in suitably stained sections the formation of intraductal

tissue from myoepithelium is easy to follow. (Masson-Goldner trichrome stain seems especially well adapted for this.) The derivation of intraductal fibrous tissue from embryonic mammary cells explains the behavior of the lobular unit. The connective tissue of a lobule takes a prominent part in cyclic changes while other fibrous tissue in the breast is not affected. When one realizes that the entire lobule, and not just the lobular epithelium is an integral part of the mammary gland, derived from the same embryonic layer, the sensitivity of all its parts to hormones is a natural corollary.

In the normal individual one would suppose a perfect balance of hormones. However, study of normal breasts shows that this hardly ever exists. In the central area beneath the nipple, lobules are normally few, and blunt ended or club-shaped ducts (to be converted to ampullae during lactation) are in evidence. Aside from this, normal breasts often contain dilated, even cystic, ducts and clusters of dilated ductules recalling the adolescent. In women past the twenties apocrine cysts are usually present.

Mammary dysplasia, as is well known, is the result of hormone imbalance, and in some of our cases, there is little doubt that a course of large doses of an estrogenic substance was the causative factor. However, one also has to suppose a sensitivity on the part of the tissue since the effect of estrogen is not the same in all individuals and varies in different parts of the same breast. The work of Pullinger is of interest in this connection. It has been known for some time that the effect of injections of estrogen varies in different strains of pure bred mice. Pullinger found that injections of estrogen following ovariectomy in a tumor-bearing strain of mice resulted in cysts, whereas in another nontumorous strain no cysts were produced. These strains were crossed and the hybrid offspring treated with estrogens. Part of each mamma reacted like one parent, part like the other, the proportions about equal. Mongrel mice showed a variety of response in all mammae much as in the human.

Some authors attribute the volume changes which take place in the breast during the menstrual cycle (8) entirely to edema. In the face of changes actually seen microscopically in many hundreds of specimens and of all we know of the effects of hormone stimulation on mammary growth, this extreme position cannot be maintained. No one would deny that edema, or better imbibition of fluid, plays a part in premenstrual swelling, but it is not the whole story. Similarly, with regard to cysts, it is easy to see that the enormous size of breast cysts relative to the ducts from which they arise, postulates growth of the duct wall and could not be due only to distention by duct contents. Actually, we know that normal lobules grow more rapidly than cancer tissue. There is then nothing impossible in the formation of cysts in a relatively short space of time. The reason for sudden distention of cysts, which certainly occurs, and for the atrophy of their lining by the pressure of fluid within them is something which needs study. One may perhaps postulate a change in chemical composition of the cyst contents or of the adjacent tissue causing sudden alteration in acid-base, water-electrolyte, and osmotic equilibria. Mechanical blockage of a duct, so long a popular explanation, cannot be invoked for many reasons, the most obvious being that dilated ducts may be associated with discharge from the nipple. A duct is usually blocked by kinking after distention, not before. We agree that concomitant factors may play a part in determining the size of a cyst, but to be formed at all there must be growth of the duct wall.

Some authors invoke congestion as the primary factor in breast alterations and even go so far as to suggest that the increased blood supply brings more hormones to the part. In any condition of hyperplasia in the breast as elsewhere there is increase in the vascular supply, but it is putting the cart before the horse to say that congestion initiates the process. Anyone familiar with the remarkably rich blood supply of even quiescent lobules in the breast would not suppose that there was a deficiency of channels for the transportation of hormones.

Where more or less normal relations are maintained between epithelium and sur-

rounding myoepithelial and fibrous tissue, although there may be distortion, the condition is mazoplasia. Should this relation be disturbed, as in papillomatosis, some other form of mammary dysplasia has supervened. The condition, instead of being a normal breast pattern occurring in a distorted fashion at an inopportune time, passes over from the aberrant physiological into the realm of the pathological. Hence the importance of radiologic diagnosis. No normal woman desires a breast operation, even a minor one. Many regard a biopsy with fear and horror and only submit to the procedure because of cancerophobia, the result of present day propaganda. It is the business of the medical profession to reduce the necessity for operation to the unavoidable minimum. The clinician and radiologist must decide whether the physiologic limit has been passed and the resulting condition needs operation.

In adenosis, if the myoid is well developed, and this is the rule in mazoplasia and in Schimmelbusch disease, we believe there is no cause for anxiety. But in adenosis in which there is epithelial but no corresponding myoepithelial hyperplasia, the possibility of carcinomatous development must be considered.

Radiologically, the picture of adenosis is far from distinct. In mazoplasia II and Schimmelbusch disease the accompanying lesions overshadow areas of adenosis in the film; this is relatively unimportant since carcinoma is unlikely in these conditions. A patch of adenosis resembles breast tissue too closely to be discerned with certainty. When it occurs as the only lesion, the breast may appear normal or the radiologist may be tempted to call it mazoplasia II or secretory cystic disease. Keeping this in mind, he should favor surgical intervention, especially of an ill-defined swelling, which corresponds to an opacity in which cysts are not clearly delineated and which is not mazoplasia I.

The radiologist who is familiar with the normal anatomy, the changes due to disturbed physiology, and the various benign pathological states affecting the breast, can offer much in the diagnosis of cyclic disturbances. There are limitations in the accuracy of differential diagnosis between benign lesions, but these limitations are not so great in segregating the benign lesions from the malignant, not discussed in this report. With clarity in pathological classification, the radiologist will eventually reach as high a level of diagnostic proficiency as he already has achieved in other domains of diagnosis.

SUMMARY

1. A simplified clinical-pathological classification of benign cyclic disturbances in the breast has been advanced to facilitate the preoperative x-ray diagnosis.

2. The gross and microscopic characters peculiar to each clinical state are correlated with the x-ray findings within the potentialities and limitations of x-ray diagnosis.

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HYPERTHYROIDISM IN PREGNANCY

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ALTHOUGH hyperthyroidism in pregnancy is not common, this complication can be a serious threat to the gravid woman and her fetus. The ample literature concerning this association attests to its importance and complexity, whether viewed from the standpoint of the obstetrician, internist, or surgeon. To clarify the situation, several questions may be appropriately posed with regard to this problem: (1) What is the effect of hyperthyroidism on pregnancy? (2) What is the effect of pregnancy on the genesis and course of hyperthyroidism? (3) What is the effect of hyperthyroidism on the developing fetus? (4) What is the preferable method of treatment of hyperthyroidism complicating pregnancy?

The purpose of this paper is to review the recent literature on this subject and to evaluate the results of treatment and the complications met in 21 pregnant patients with hyperthyroidism, in an attempt to answer the questions raised. All of the patients considered were examined and followed by members of the Thyroid Clinic and of the Division of Obstetrics and Gynecology of the University of California Hospital between the years 1937 and 1950, inclusive.

The ages of the patients varied from 21 to 37 years; a mean of 27.6 years. We have classified the clinical severity of hyperthyroidism as mild in 5, moderate in 12, and severe in 4 (Fig. 1). Ocular signs typical of Graves' disease were present in 8 of our 21 patients. The basal metabolic rates of the patients studied ranged from +12 to +69 per cent. The protein-bound serum iodine varied in our patients from 7.9 to 15.9 micrograms per cent. (Normal range in our laboratory is from 4.0 to 8.0 micrograms per cent in nonpregnant women.)

The incidence of hyperthyroidism in pregnancy has been reported as varying from 0.016 per cent to 1.4 per cent of all pregnancies (Table I). In this clinic, the incidence of hyperthyroidism is 0.175 per cent, or 21 in 11,390 pregnancies.

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WHAT IS THE EFFECT OF HYPERTHYROIDISM ON PREGNANCY?

The effect of hyperthyroidism on pregnancy can be appraised by considering the fate of patients prior to the advent of modern therapy. In 1913, Seitz reported that in his series of 112 cases of hyperthyroidism in pregnancy (collected from a number of sources), 11 premature labors occurred, 3 patients miscarried, and 3 macerated fetuses were passed. Seven patients died. Spontaneous abortion, premature labor, fetal death in utero, and stillbirth, most authors agree, may be complications of hyperthyroidism in pregnancy. Violent labor and postpartum hemorrhage have also been described in the woman with toxic goiter (42).

The insecurity of an early pregnancy may depend upon many factors. The largest group of abortions, Mall, and Hertig and Livingstone insist, falls into the defective germ plasm category. Nevertheless, in approximately 15 per cent of abortions (19), maternal factors, including hyperthyroidism, are said to affect a pregnancy adversely. This may be because of local uterine or general systemic causes. Obviously, the correction of such maternal factors prior to pregnancy is indicated (4). If pregnancy supervenes, however, the maternal factors should still be rectified, especially if such correction will increase the likelihood of normal, full-term delivery and a healthier mother. Gudernatsch demonstrated that thyrotoxic abortion was common in the rat. This has also been shown to hold for guinea pigs (21) and rabbits (25). On the other hand, Mussey and associates (32), Lahey, and Clute and Daniels hold that human abortion and fetal abnormality are not more frequent in hyperthyroidism, or hyper-

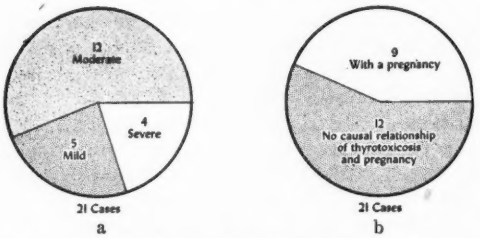

Fig. 1. a, Indicating severity of hyperthyroidism in cases reported. b, Onset of hyperthyroidism.

thyroidism treated by subtotal thyroidectomy, than in normal pregnancy.

Spontaneous abortion occurred in 4 of our cases. One patient aborted on the second and another on the third postoperative day after thyroidectomy. These patients were in the second and third trimester of pregnancy. Another pregnant patient who had received radioactive iodine for hyperthyroidism prior to the diagnosis of pregnancy aborted at approximately the fourth month of gestation. However, definite hydrops fetalis in this patient is considered to have been due to Rh isoimmunization and not to thyrotoxicosis or its treatment. One tubal abortion in the first trimester was obviously not due to maternal hypermetabolism or to its therapy.

It is curious that in 2 of the 3 cases of therapeutic abortion performed because of serious hyperthyroidism in pregnancy, the placenta showed necrosis or hydropic degeneration. This, in our opinion, would have been followed in a short time by spontaneous abortion, had the pregnancy been allowed to proceed. We were not able to establish whether the hyperthyroidism or thyroidectomy, effected approximately 1 week before, was responsible for the chorionic abnormality. Excessive bleeding, either at the time of miscarriage, abortion or term delivery, did not occur in any of our patients. Subsequent normal term deliveries occurred in later years in at least 10 of our group of 21 patients after control of their hyperthyroidism.

TABLE I.—INCIDENCE OF HYPERTHYROIDISM IN PREGNANCY

Author	Year	Region	No. of pregnancies	No. of cases of hyperthyroidism in pregnancy	Per cent incidence
Bustos Morón (7)	1935	Buenos Aires	30,000	5	0.016
Portis and Roth (35)	1939	Chicago	1,000	14	1.4
Wallace (40)	1940	New York	11,571	4	0.039
Javert (22)	1940	New York	23,439	18	0.076
Baumgartner (2)	1942	Los Angeles	1,585	22	1.39
McLaughlin and McGoogan (29)	1942	Omaha	6,112	19	0.31
Davis (13)	1944	Baltimore	20,000	8	0.04
Kibel (24)	1944	New York	15,864	12	0.075
Ciulla (9)	1949	Pavia	10,202	18	0.176
Dailey and Benson	1951	San Francisco	11,390	21	0.175

WHAT IS THE EFFECT OF PREGNANCY UPON HYPERTHYROIDISM?

Since hyperthyroidism usually progresses in severity and may be somewhat cyclic, it is difficult to ascribe an exacerbation of thyrotoxicosis to the pregnancy. Most authors feel that pregnancy does not initiate an aggravation of thyrotoxicosis, although Ciulla and Theilhaber hold the contrary view. Our data do not support the concept that pregnancy has an identifiable deleterious effect upon hyperthyroidism

Among our 21 patients, 12 dated the onset of the hyperthyroidism from the pregnancy under study or a previous pregnancy. Gardiner-Hill reported that in 8 of 71 patients the onset of Graves' disease was concurrent with pregnancy. Clute and Daniels believe pregnancy plays no role in the development of hyperthyroidism.

WHAT IS THE EFFECT OF HYPERTHYROIDISM ON THE DEVELOPING INFANT?

No particular developmental fetal abnormality is known to be caused by maternal hyperthyroidism, and there are no placental aberrations definitely attributable to the hyperactive maternal thyroid. We believe there is no convincing evidence that hyperthyroidism per se will result in abnormalities in the infant. Clute and Daniels share our opinion that hyperthyroidism does not affect the fetus adversely. The children delivered in all our cases of hyperthyroidism complicating pregnancy were normal, and all but 1 survived. This baby, a deadborn infant, was

delivered 2 months after thyroidectomy. There were no obstetrical difficulties or errors encountered. The mother received only 1 small dose of a barbiturate during the entire labor of 8 hours, and local anesthesia was employed during an easy delivery. The placenta was normal.

Infant damage, however, has been reported from the effects of radioactive iodine, thiouracil, and related compounds used in the treatment of hyperthyroidism. Support for this view is the work of Chapman and associates, who have demonstrated that radioactive iodine is picked up by the fetal thyroid as early as the fourteenth week of gestation. Hone and Magarey have reported the birth of a cretin whose mother had received methylthiouracil for thyrotoxicosis during her pregnancy.

WHAT IS THE PREFERABLE METHOD OF THERAPY OF HYPERTHYROIDISM COMPLICATING PREGNANCY?

The adequate care of patients whose pregnancy is complicated by hyperthyroidism presents a problem both in diagnosis of milder degrees of thyrotoxicosis and in therapy. Difficulty in diagnosis of minimal thyrotoxicosis during pregnancy is due to numerous factors: symptoms of anxiety may superficially mimic those of hyperthyroidism; enlargement of the thyroid usually occurs during pregnancy; and laboratory aids are of limited value. The basal metabolic rate rises during normal pregnancy, as does the protein-bound iodine content of the serum. Hyperthyroidism may not always be apparent, but the physician should consider this diagnosis when the gravid woman reports "nervousness," excessive perspiration, palpitation, looseness of stools, and failure to gain weight despite generous food intake.

Certain of the orthodox methods employed in treating hyperthyroidism are undesirable in pregnancy. At the University of California Hospital nonpregnant hyperthyroid patients are treated either by (1) long term use of antithyroid drugs, (2) subtotal thyroidectomy preceded by medical preparation with iodine and antithyroid drugs, (3) x-ray, or (4) radioactive iodine therapy.

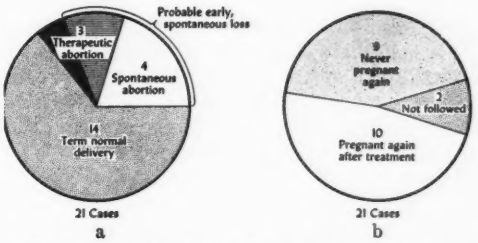

Fig. 2. a, Showing fate of pregnancy. b, Pregnancy subsequent to control of thyrotoxicosis.

An exceedingly small number of our patients have received thiouracil or related compounds as the only definitive treatment of hyperthyroidism. We believe that close follow-up is not feasible when patients come from remote areas and when the likelihood of recurrence is great. Subtotal thyroidectomy is advised for all patients with toxic nodular goiters. Social and geographic reasons are frequently cogent indications for surgery. X-ray therapy, in general, has been reserved for early mild hyperthyroidism or postoperative recurrences, especially when complicated by vocal cord paralysis or hypoparathyroidism. Finally, therapy with radioactive iodine has been given on an experimental basis to patients with diffuse toxic goiters, especially when the possibility of progressive exophthalmos exists. In this latter instance, it is desirable to avoid surgery if possible.

When hyperthyroidism is associated with pregnancy, several of the methods of therapy mentioned are inappropriate. Since the antithyroid agents cross the placental barrier and may affect the fetal thyroid, it would seem prudent not to administer them when pregnancy is known to exist. Several authors have reported scattered instances of the use of drugs of the thiouracil type in pregnant women without ill effects on the infant. These reports do not allow conclusions regarding the safety of these agents. Cretinism has been reported and the infant's thyroid showed vascular engorgement, enlargement, hyperplasia of the acini and increased fibrous tissue overgrowth (20). However, Bell has performed an invaluable service by his demonstration, in a series of 21 pregnant patients with hyperthyroidism, that drugs of the thiouracil type

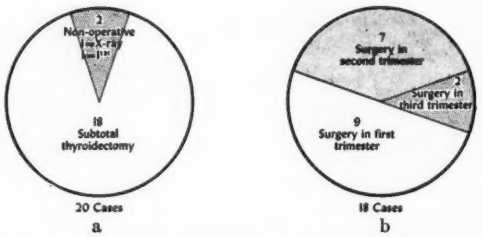

Fig. 3. a, Indicating method of treatment. b, Time of surgery during pregnancy.

may be given with safety as a preoperative preparation measure. This author's views, which we share, are that the hyperthyroidism must be promptly controlled, but it is undoubtedly true that many thyrotoxic patients may be adequately prepared for surgery with iodine alone. Williams and associates have reported that thiouracil may be transmitted to the nursing infant through the milk of a mother receiving this antithyroid drug. Radioactive iodine is even more potentially harmful to the developing fetal thyroid and is hence clearly contraindicated (31).

Medical treatment in our series consisted usually of the administration of sedatives and Lugol's solution from 9 days to 3 months. Thiouracil was given to 1 patient for 17 days only, and propylthiouracil had been given to 1 patient for 6 months prior to acceptance in this clinic. In 1 patient, in whom pregnancy had not been diagnosed, 400 microcuries of radioactive iodine were given. Another patient with undiagnosed pregnancy was given 2,700 roentgens of x-radiation. Subtotal thyroidectomy was performed after adequate medical preparation in 19 patients between the first and seventh months of pregnancy. All patients in our series, treated medically or surgically, recovered from their thyrotoxicosis. One patient required subsequent x-radiation postpartum to effect a complete cure. Five patients are known to be taking desiccated thyroid as prescribed by their local physicians, and hence may be presumed to be hypothyroid. This incidence, however, is not significantly greater than the expectancy of hypothyroidism in our clinic following thyroidectomy for toxic goiter in nonpregnant women (17).

A knowledge of the effects of hyperthyroidism on the gravid woman and her fetus is vital for the proper understanding and appropriate management of thyrotoxicosis complicating pregnancy. It is not settled whether hypermetabolism is a cause of infertility, but it is probable that hyperthyroidism, as well as hypothyroidism, contributes to difficulty in conception by virtue of frequent anovulatory cycles (6). Hyperthyroidism accentuates the increased metabolism of pregnancy. It may lead to complications as serious as cardiac failure in the pregnant woman. It also may cause decreased coagulation of blood and lead to a tumultuous or premature labor and postpartum hemorrhage (38, 42). Otherwise, hyperthyroidism does not seem to influence the normal course of established pregnancy.

The cause of toxemia of pregnancy is still sought. Hypothyroidism has been considered at least a contributory cause of toxemia (1, 5, 11), and it is not entirely surprising that hyperthyroidism has also been linked with the production of the eclamptogenic toxemias (22, 38). It is true that hyperthyroidism causes a rapid diminution in the glycogen stores in the liver and increases the ketone bodies in the urine. Hyperadrenalism, with a decreased insulin effect, is also noted. Theoretically then, these factors might encourage the development of a toxemia of pregnancy, or might exaggerate a mild pre-eclampsia, which under ordinary circumstances would not reach serious proportions. Kibel reported toxemia in 5 of his series of 8 pregnant patients whose course was complicated by hyperthyroidism and who went to term. Javert described toxemia in 10 of 13 patients attaining at least the thirty-seventh week of pregnancy. McLaughlin and McGoogan mentioned toxemia in 5 of 8 patients in the last trimester of pregnancy complicated by hyperthyroidism. Other authors do not stress the association of toxemia of pregnancy and toxic goiter. In our clinic the incidence of toxemia of pregnancy was only 2.9 per cent (1946–1950), yet none of our patients with thyrotoxicosis presented an eclamptogenic toxemia. One patient had a hypertension before pregnancy, but this was not aggravated by the gestation or the hyperthyroidism.

It is true that no standardized therapy is desirable or practicable in clinical medicine, but the consensus of many authorities is that, when pregnancy is complicated by hyperthyroidism, the treatment of choice is subtotal thyroidectomy (3, 10, 12, 14, 24, 27, 30–32). There are only a few authors who would avoid surgery (9, 15, 22).

COMMENT

It is our opinion that during pregnancy the most appropriate treatment of maternal hyperthyroidism is medical preparation with iodine, followed by subtotal thyroidectomy. This view, however, might be modified if the Graves' disease is exceedingly mild when first encountered—particularly when the patient is early or late in pregnancy. Then iodine alone, or with x-radiation, might be initiated. However, the time required to effect a cure with roentgen therapy averages 7 to 8 months (37). If the pregnancy has advanced beyond the period of viability and the thyrotoxicosis is severe, medical treatment should be instituted, and if surgery is required, thyroidectomy should be performed even though the patient is undelivered.

Medical consultation frequently emphasizes the psychosomatic phases of hyperthyroidism and stresses the undesirability of adding a pregnancy to an already complicated picture. Frequently, therefore, pregnancy is interrupted when a patient with a thyrotoxicosis becomes gravid. The justification for this radical attitude has usually been purely theoretical. One cannot deny that pregnancy carries with it additional emotional problems, uncertainties, and morbid fears which may upset the precarious balance of an unstable personality. Hyperthyroidism undoubtedly imposes an additional physical and emotional strain upon the woman. Today, however, the woman's life and ultimate health, we think, are rarely in serious jeopardy.

Obstetrical opinion regarding therapeutic abortion has become more conservative in recent years (33). With the advent of improved medical therapy, better anesthesia and surgery, it is probable that therapeutic abortion is almost never justified in hyperthyroidism complicating pregnancy. A review of our cases treated at the University of California Hospital, in the light of more recent developments and better defined obstetrical attitudes, strengthens this conclusion. For example, it is difficult now to justify an abortion done several days or even a week after thyroidectomy, despite the fact that such patients obviously were seriously ill, complicated gravidas. A resort to abortion reveals a lack of confidence in the surgical and medical control of hyperthyroidism. The exceptions might be cases, such as that of Portis and Roth, in which repeated surgery on the thyroid precluded the likelihood of a successful operation, or in which surgery is contraindicated for other reasons and medical management has been unsuccessful in controlling the hyperthyroidism.

The fetal salvage has not been satisfactory in hyperthyroidism complicating pregnancy. It has been suggested that an important factor in the support of pregnancy is the maintenance of adequate circulating thyroid hormone (23, 34). In our clinic, 1 patient in 5 upon whom subtotal thyroidectomy is performed becomes hypothyroid. It is logical, therefore, to consider the administration of thyroid extract to certain obstetrical patients postoperatively until delivery, in an effort to avoid abortions secondary to hypothyroidism (3). The most accurate means of determining the need for supplementary thyroid medication is obtained from the level of protein-bound iodine. This level, together with the basal metabolic rate, is usually elevated in normal pregnancy. Consequently, the gauging of the dosage of thyroid extract should be governed accordingly.

Inasmuch as spontaneous abortion ordinarily occurs most frequently during the early months of pregnancy, it would also seem best to postpone subtotal thyroidectomy, if possible, until at least the second trimester.

SUMMARY AND CONCLUSIONS

From a study of 21 cases of hyperthyroidism complicating 11,390 pregnancies, and a review of the recent literature, the following answers to the stated questions seem reasonable:

1. What is the effect of hyperthyroidism on pregnancy? There is no demonstrable ad-

verse effect on well established pregnancy. No increase in the incidence of toxemia of pregnancy or postpartum hemorrhage is to be expected because of hyperthyroidism per se.

2. What is the effect of pregnancy on the genesis and course of hyperthyroidism? Pregnancy appears to be a significant factor in the initiation, or at least the time of onset of hyperthyroidism. However, pregnancy does not appear to alter appreciably the course of toxic goiter.

3. What is the effect of hyperthyroidism on the developing fetus? There is a slight increase in fetal loss during early pregnancy; however, there is no fetal or placental abnormality secondary to hyperthyroidism.

4. What is the preferable method of treating hyperthyroidism complicating pregnancy? In general, we recommend as the procedure of choice: subtotal thyroidectomy preceded by adequate medical preparation, including iodine but without thiouracil compounds. Surgery should best be performed, if possible, after the first trimester. Adequate levels of thyroid hormone should be maintained at all times to insure the maintenance of the pregnancy.

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AN ANALYSIS OF ONE HUNDRED CASES OF SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

Part II. With Special Reference to its Theoretical Curability

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ALTHOUGH dysphagia must be considered a relatively late symptom of carcinoma of the esophagus, this symptom remains the "earliest" universally recognizable danger signal of this disease. Because of the definiteness of this symptom, it is possible in most cases to ascertain the onset of symptomatology referable to the esophagus with reasonable accuracy. Until recent years, the mortality of carcinoma of the esophagus was essentially 100 per cent. As a consequence, considerable information has accumulated concerning the history of the disease, the incidence of nodal metastases, and complications at the time of autopsy. Concerning the latter items there is a considerable variance in the findings of different authors. However, with regard to the life expectancy of the individual so afflicted, it is generally agreed that after the appearance of dysphagia, with few exceptions, untreated carcinoma of the esophagus appears to be a rather rapidly fatal disease.

On the basis of the reports in the literature, it has been observed that the patient with carcinoma of the esophagus (adenocarcinomas included) has an average life expectancy from the onset of symptomatology until death varying from 7 months (2), 9.5 months (8), 10.5 months (13), to 12 months (4). These figures pertain to untreated patients or patients given palliative therapy such as bougienage, intubation, or gastrostomy. It has been demonstrated that such palliative efforts exert no significant effect in the prolongation of life, although the value of these procedures in certain instances is unquestioned.

The average patient with this disease by the time the diagnosis has been established has utilized at least 5 months (6) of his average life expectancy. The assumption may be made that such patients are essentially ante mortem with widespread metastatic disease or an equally fatal complication. However, it has been noted time and again at autopsy that localized "curable" esophageal tumors are not uncommon. This fact suggests that many of these patients die not of inoperable complications but of starvation and dehydration due to the inability to swallow or the lack of desire to do so because of the associated discomfort. The incidence of localized esophageal carcinomas without nodal involvement at the time of autopsy in previously reported series varies from 19 per cent (3), 25 per cent (2), 28.6 per cent (1), 40.7 per cent (9), to 48 per cent (13, 14).

On the other hand, Tomlinson and Wilson reported 100 per cent nodal involvement in 50 cases. Vinson has stated that "metastatic nodules are found at postmortem examination of almost all subjects having esophageal carcinoma even though death may have occurred following some operative procedure and not as the result of carcinoma." As recently as 1944 Steele stated that "the outlook for a patient with carcinoma of the esophagus is indeed gloomy because we are dealing in the majority of cases with a poor half-starved old man with a growth which has already spread to his vitals. Realizing this, we can merely try to relieve his dysphagia without attempting to cure his growth. . . ."

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Recently, the authors have published (7) an analysis of 100 cases of carcinoma of the esophagus in which a special study was made of the delay periods and delay factors in the diagnosis and therapy of this disease. Only squamous cell carcinomas were included. This series is not comparable to previously reported series which have included adenocarcinomas. Undoubtedly, many of the latter represent carcinoma of the stomach with esophageal extension.

A contrasting study was presented of the delay periods and factors in 50 patients referred to a state institution versus an additional 50 patients attending city and county institutions. It was observed that the indigent city and county patient reached his hospital of definitive therapy on an average of 87.4 days after the onset of symptomatology referable to the esophagus. The outstate patient, who, of necessity, was referred by a practicing physician to the state institution arrived at his hospital of definitive therapy on an average of 168.1 days after onset of symptoms. The number of days required for the state institution to establish the diagnosis after the initial outpatient visit averaged 2.9. In the city and county patient, an average of 34.4 days was required for the establishment of the diagnosis from the day of the patient's first outpatient visit.

Therefore, the average delay period from the onset of esophageal symptoms (dysphagia) until the diagnosis was made was 171 days in the state institution patients and 122 days in the city and county patients.

An average of 24.7 days from the date of diagnosis until definitive surgical intervention was necessary for the preoperative preparation of the patient. This average preparation period is available in the state institution series only. Consequently, an average of 195.8 days (6.5 months) elapsed in this group of patients from the date of onset of esophageal symptoms until the patient was actually on the operating table.

The conflicting reports relative to the presence or absence of important complications at the time of death in such patients have been alluded to earlier. Accurate information concerning this point should be of importance to the surgeon. From such data the theoretical curability of the lesion should become apparent. Because of these conflicting reports and the appearance in the literature recently expressing defeatism (5) concerning the curability of such patients, this study has been extended for the express purpose of assaying the curability of these 100 cases of squamous cell carcinomas in whom the actual delay periods already are known.

SOURCE OF MATERIAL

A total of 100 cases of squamous cell carcinoma of the esophagus were studied. Fifty were obtained from the files of the University Hospital, Minneapolis (state institution). An additional 20 were obtained from the Minneapolis General Hospital (city institution), and 30 more cases were obtained from the Ancker Hospital, St. Paul, Minnesota (city and county institution). The cases were obtained consecutively from 1948. Because of the fact that these cases have been obtained from three different institutions, the majority fell within the period when esophagogastrectomy with the restoration of gastrointestinal continuity was an accepted procedure. Only squamous cell carcinomas of the esophagus have been included in this study.

ANALYSIS OF CASES

In this series of 100 cases (city and county and state cases included), it has been shown that the average delay from the onset of symptoms until the diagnosis was established was approximately 5 months. It is impossible to estimate the age of the lesion before symptomatology was produced. In any event, from the previously reported material, the average life expectancy of this group from the time of the establishment of the diagnosis until death is 2 to 7.5 months. Therefore, the cases in this series are relatively late. No data are available of the interval from the time the diagnosis was established until death occurred.

In the final analysis of these 100 cases of squamous cell carcinoma, autopsies were performed in 79. In an additional 15 cases surgical exploration only was carried out.

TABLE I.—FINAL ANALYSIS OF 100 CASES OF CARCINOMA OF THE ESOPHAGUS

	No. autopsies or operation and autopsy	No. operation only	No. neither autopsied nor operated upon	Per cent
Localized "curable" lesions	22	4	*	26*
Metastases Regional only	5	3		8
Distant	28	3	1	32
Local invasion of adjacent structures	13	6		19
Perforation Local	4	2	1	7
†Fistulas	12‡	1	1	14

*Three cases were clinically operable without evidence of any complication; however, they are not included in the total.
†Fistulas: Tracheoesophageal, 5; bronchoesophageal, 4; pleuroesophageal, 3; mediastinoesophageal, 1; site not stated, 1.
‡One case followed esophagoscopy.

In 6 patients neither autopsy nor exploration surgically was done (Table I).

A most significant finding was the fact that in 22 autopsied cases, the lesion was localized without any evidence of nodal involvement nor important local spread and, therefore, was "curable." An additional 4 cases in a similar stage were established by surgery. Furthermore, there were 3 cases clinically operable without evidence of any complication. However, these latter patients were subjected neither to surgery nor to autopsy and have not been included in this category. Therefore, in 26 cases (26 per cent) a localized and "curable" lesion was present at the time of death or operation.

In addition, in the autopsied group, there were 5 cases exhibiting regional metastases only, metastatic nodes which ordinarily would be resected with the presently conceived radical operation. Likewise, 3 more patients subjected to surgery only, fall into this same category. Therefore, a total of 8 cases are recorded of regional metastases without evidence of any other complication.

Some criticims may be justifiable concerning the inclusion of these cases with operative findings only. While it is true that at the time of exploration the operator may have overlooked some small areas of tumor, in studying these protocols, it was felt that a satisfactory exploration had been done.

On the other hand, in 28 cases evidence of distant spread was noted at autopsy; in 3 additional operative cases a similar complication was revealed. One patient, neither autopsied nor operated upon, had distant metastases. Therefore, 32 cases (32 per cent) exhibited distant metastases which contraindicated major surgical intervention.

In 19 cases by autopsy and operation local invasion of adjacent structures was revealed. Six cases at autopsy or surgery exhibited a local perforation of the tumor. There was an additional patient, neither autopsied nor subjected to surgery, who evidenced a similar situation.

Fourteen patients were observed to have a fistulous tract between the esophagus and the respiratory tract. Twelve were discovered at autopsy; 1 at operation; 1 other patient, subjected to neither autopsy nor surgery, had obvious clinical signs of this complication.

It is apparent from these figures that certain cases exhibited more than one of the major complications listed.

THE THEORETICAL "CURABILITY" OF CARCINOMA OF THE ESOPHAGUS

By further breaking down these figures, one may approximate the theoretical "curability" of carcinoma of the esophagus. A separate table (Table II) has been made listing those situations in which a cure may be possible.

It is of considerable import that in 26 cases at operation or autopsy localized lesions were revealed. In 8 additional cases regional nodal metastases were noted. Therefore, 34 patients (34 per cent) at the time of death or operation had theoretically "curable" lesions. Twenty-seven of these 34 patients had been subjected to autopsy.

Moreover, in this table, additional categories have been included, wherein one may expect to salvage an occasional case. (Invasion of adjacent structures, 3 cases; local perforation, 3 cases; bronchoesophageal fistulas, 4 cases.) The complications listed are considered usually to represent inoperability and nonresectability in patients with carcinoma of the esophagus. Each case listed was

otherwise uncomplicated except for the complication described. All cases are examples of an apparent locally infiltrating lesion without evidence of distant spread.

In the therapy of abdominal carcinoma, the general surgeon has no hesitancy in sacrificing juxtapositioned involved organs en masse. In selected patients, the combination of pneumonectomy with esophageal resection might be considered. Also, perforation per se would not appear to be a contraindication to excision. The complications of the involvement of vital structures deserve additional comment. It is realized that at times it is impossible for the surgeon at operation or the pathologist at autopsy (without serial sections) to determine whether or not there is actual involvement of adjacent vital structures. All are aware of the inflammatory process which precedes carcinomatous invasion and the difficulties encountered in determining where tumor ends and normal tissues begin. It would appear from the autopsy findings that some of these latter cases, though the number may be small, with complications usually considered to be inoperable and nonresectable may represent an opportunity for a more radical attempt.

TABLE II.—"CURABILITY" IN 100 CASES OF CARCINOMA OF THE ESOPHAGUS

	No. of cases	Per cent
Localized "curable" lesions	26	
Regional metastases only	8	34
*Invasion of adjacent structures	3†	?
*Perforation	3	?
*Fistulas	4	?
Clinically operable; neither autopsy nor operation	3	—
		34

*In cases listed here, credit was given only to the category which represented the most serious lesion to the patient.
†One case was resected. Anastomosis was made above the arch of the aorta at the apex of the chest. The tumor was intimately adherent to the arch of the aorta and right lung. The patient is alive and well without evidence of recurrence 6 years postoperatively.

DISCUSSION

The theoretical "curability" of squamous cell carcinoma of the esophagus is, of course, an entirely different problem than the actual curability of this lesion. A 34 per cent theoretical "curability" appears to be considerably higher than the present day surgical experience would indicate. However, this series is composed entirely of the squamous cell type. As such, this series cannot be compared with other reported studies in which adenocarcinomas of the lower esophagus have been included. A second factor which may affect this figure is related to the autopsy material from which it was obtained. The material was obtained from routine autopsied cases in which no special study of esophageal carcinoma was contemplated. Consequently, no special attempt was made to study an unlimited number of nodes for metastasis. Certainly, gross nodal involvement was identified. However, microscopic or microanatomic nodal involvement may have been overlooked. The autopsies were performed in a university center under the supervision of competent individuals. Consequently, the findings as such represent the true situation within the limitations of any study of routine autopsy material.

Radical resections for carcinoma of the esophagus are of relatively recent origin. Few surgeons have had a sufficiently large enough series to determine the actual curability of this lesion. The actual curability in contrast to the theoretical "curability" will be affected by the following three major considerations: (1) the presence of concomitant disease, (2) the age of the patient, and (3) the operative mortality.

The average age of the patient with carcinoma of the esophagus is 62 years. This is somewhat above the average of most patients with a malignant lesion. The older the patient the greater is the incidence of concomitant disease processes, particularly diseases of the major systems, viz. cardiovascular, pulmonary, and renal. In view, of the magnitude of the operative procedure, certain patients with "curable" lesions will be rejected as unsatisfactory surgical risks. The exact number is problematical. Nevertheless, this factor will affect in an adverse fashion the actual curability of the lesion.

The second factor is related to the first. A perusal of actuarial statistics revealed that the individual aged 62 years has an average

life expectancy of 13.27[1] years. Furthermore, 19.95[1] per cent of individuals aged 62 years will die mainly of other diseases during the 5 year follow-up period. Some patients with carcinoma of the esophagus are included; however, the incidence is small and the percentage would be affected only slightly by correcting for this factor.

The third factor to be considered is the operative mortality. In good hands, the mortality of radical esophagogastrectomy with the restoration of gastrointestinal continuity is presently in the neighborhood of 20 per cent. Assuming that the operative mortality will affect equally all patients operated upon, one-fifth of those patients with curable lesions will succumb to the operation.

Therefore, on the basis of the operative mortality and life expectancy figures alone, the percentage of patients theoretically "curable" (34 per cent) would be reduced by 39.95 per cent to a potential 5 year cure rate of 20.4 per cent. This possible 5 year cure rate would be worsened further by two intangibles: (1) the number of patients rejected for surgery because of concomitant disease processes unrelated to, but possibly adversely affected by, a carcinoma of the esophagus; and (2) the fact that the percentage of theoretically "curable" lesions herein recorded is higher than the actual situation.

On the other hand, it is anticipated that overall longevity will increase. Also, that a further reduction in operative mortality can be anticipated. Considerable knowledge is accumulating with regard to the safe management of elderly patients through major surgery. Further advances are being made in the development of newer and more effective antibiotics. It is hoped that patients will be seen by the proper individuals in an earlier stage of their disease process. Nevertheless, the problem of important improvement in actual cure rates for this disease is related to the problems of the patient aged 62 years with concomitant disease, a result of the normal aging process.

SUMMARY

1. One hundred cases of squamous cell carcinoma of the esophagus have been studied.

2. Thirty-four patients (34 per cent) have exhibited localized "curable" lesions at autopsy and/or surgery. In 8 cases of this group, regional lymph nodes were positive.

3. An additional 10 patients exhibited local complications, usually considered to represent inoperability, without signs of distant spread. A salvage rate, though small, would appear to be attendant in a bolder surgical attempt in selected cases.

4. Factors affecting the actual curability in relationship to theoretical "curability" are discussed.

[1]Commissioner's Standard Ordinary Table of Mortality, 1941.

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EDITORIALS

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ARTERIAL GRAFTS

". . . blood of man
That swift as quicksilver . . . courses through
The natural gates and alleys of the body."
Edward de Vere
(Hamlet)

WORLD War II, with its many vascular injuries, again focused surgical attention on the great need for a technique to bridge a defect in a major artery with preservation of the arterial blood flow. The rapid growth of the surgical treatment of congenital and acquired cardiovascular defects during the period immediately following the war provided a continuing impetus for the elaboration of such a technique. It is now fair to state that the technical aspects of this problem have been largely overcome, and a great variety of arterial lesions may now be successfully repaired with preservation of blood flow.

Among the variety of agents evolved for grafting an arterial defect are: (1) an autogenous vein, (2) an autogenous vein wrapped with fascia, (3) a highly polished plastic prosthesis, (4) an artificial tube of fibrous tissue (pericardium), (5) a formalin or alcohol fixed segment of homologous or heterologous artery, and (6) a cold-preserved or lyophilized segment of homologous artery. Although all of these methods have met with a considerable degree of success, the most practical method giving the most consistent and uniformly favorable results is the use of the preserved arterial homograft.

To Pierce, working in Gross's laboratory should go the credit for reintroducing the arterial graft. Although Carrel and Guthrie, at the turn of the century, had demonstrated experimentally the successful use of such grafts, clinical and experimental interest in the problem had remained dormant. Since 1948, however, many surgical laboratories across the country have been studying this method vigorously.

One of the major problems relating to the clinical use of the arterial homograft (transplantation of an arterial segment from a donor of the same species) is that of availability. The grafts must be obtained sterile from young individuals, from 2 to 35 years of age, previously in good health, who die a sudden or relatively acute death. The vessels must be obtained within 6 hours postmortem. Since these conditions involve relationships with the patient's relatives (permission), coroner's office (medicolegal aspects), and morticians (embalming), and since the time limitation is strict, the procurement of an adequate supply of segments for the "artery bank" is often difficult, even in large communities. The panel of eligible donors may be increased in communities where high voltage cathode ray irradiation, in the order of magnitude of 2.0 or 2.5 roentgen equivalent phys-

ical units delivered to frozen vessels, can be employed to sterilize segments obtained from unsterile autopsy material. Such machines, however, are not widespread.

The problem of storage is equally important. The fresh arterial segment, transplanted immediately after death of the donor, appears to be the most desirable graft and, barring technical mistakes, yields almost 100 per cent successful results. To preserve grafts for a long period in a condition which corresponds as closely as possible to the fresh state would appear to be the goal of the storage method. Preservation in a fluid medium consisting of a balanced salt solution containing 10 per cent plasma or serum in an icebox at 4 degrees C. accomplishes this aim for periods up to about 45 days. Gross found that tissue culture viability disappeared and the percentage of failures of aortic grafts increased rapidly after this period, although we have had successful experimental and clinical results up to 6 months of storage. This storage method therefore suffers the defect of being satisfactory for only a short period of time, thus requiring frequent replacement of a commodity hard to procure.

"Deep" freezing of arterial grafts has been shown to be successful in the experimental laboratory by Hufnagel and by Deterling. The former froze the grafts dry at −196 degrees C. (liquid nitrogen) and stored at −74 degrees C. (carbon dioxide); the latter froze dry at −74 degrees C. and stored at −27 degrees C. (commercial deep-freeze unit). Recently we have shown that vessels frozen rapidly at low temperatures, either −78 degrees C. or −196 degrees C., if frozen in nutrient media and thawed rapidly, retain their capacity to grow in tissue culture. Tissue culture studies also suggest that a low (−78 degrees C.) storage temperature is superior to that of the commercial deep freeze (−27 degrees C.). It seems probable that grafts may be kept almost indefinitely in a condition approximating the freshly obtained vessel if rapidly frozen in nutrient media at −78 degrees C. and stored at the same temperature. Recently, also, lyophilization has been suggested as a method of preservation. This technique has the merit of simplicity, of storage at room temperature, and of transportability of the graft. Much work remains to be done, however, to evaluate the consistency of success which may be expected from the use of lyophilized grafts.

Suture anastomosis is best suited for insertion of the graft. This may be done by temporarily controlling blood flow proximally and distally with noncrushing arterial clamps during the anastomoses; or, if preservation of blood flow during the procedure is essential, as for example in the carotid artery, the technique of "minimal interruption" over a temporarily placed polythene tube may be employed. All the niceties of technique of vascular suture—strict asepsis, avoidance of tissue injury by trauma or desiccation, careful stripping of the adventitia, careful placement of small atraumatic sutures, careful wound closure without dead space or necrosis—must be meticulously observed. In addition, the employment of a graft of proper size is of paramount importance. The lumen of the graft, when distended by the blood pressure, must match as exactly as possible the lumen of the recipient vessel, thus forming a vessel in continuity of uniform or tapering caliber. If either anastomosis forms a constriction, or if the graft distends, thus creating a sudden change in the size of the vessel, turbulence and eddy currents are created which strongly favor intraluminal thrombosis and failure. For the same reason, if a long graft is employed which must traverse a circuitous route, all curvatures should be gradual and no sharp

angulations permitted. If these precautions are observed, anticoagulant drugs need not be used, unless blood flow has been interrupted for a period of over an hour. If interruption has been prolonged, thrombosis of the distal arteries may occur, and heparin should be used to limit the spread of these distal thromboses.

The limitations on the size of artery suitable for grafting and the length of graft have not been clearly established. All arteries with an internal diameter of 3 millimeters or larger may be successfully grafted; it is probable that smaller ones may also be suitable but with less certain results because of technical difficulties. The maximum safe length for a graft is not certain, but relatively long ones (6 to 10 inches) have been used experimentally in the aorta of dogs. We have successfully transplanted clinically an aortic graft 5 inches and a femoral graft 3 inches long. It is possible that the length of graft which can be safely used may prove to be a function of its diameter.

The fate of these homografts is particularly interesting. All cellular elements in the graft are destroyed by host reaction by the end of the third week; the elastic tissue of the media, however, persists for a period of at least 2 years. An inflammatory reaction around the graft results, at 1 month, in a firm fibrous tissue outer layer. Meanwhile, the host is elaborating a new inner layer which grows in from each end of the graft, ultimately entirely lining it. At first primarily fibrocellular, this layer later undergoes remarkable differentiation; the inner cells assume endothelial forms and new elastic fibrils are laid down. Spotty or diffuse calcification may occur in this layer. Thus the host builds a new blood vessel on the scaffold of the elastic tissue of the graft.

The clinical potentialities of this technique are multiple. We have successfully used grafts in the treatment of the following lesions of arteries: coarctation of the aorta, mycotic aneurysm of the thoracic aorta, arteriovenous fistula (femoral), posttraumatic false aneurysm (femoral and axillary), acute traumatic injury (femoral), and malignant neoplasm invading an artery (femoral). In addition, Gross has used grafts to create shunts in cyanotic children when a suitable systemic artery was not available for anastomosis. Some arteriosclerotic aneurysms (ilial, innominate, lower aortic) may occasionally prove to be resectable. The implications to military medicine in the treatment of arterial battle injuries are obvious. The technique offers real promise in enlarging the scope of the operative attack on malignant disease in instances in which close proximity to or invasion of a vital artery by the neoplasm heretofore has precluded adequate resection. Arterial ligation which threatens loss of tissue distally or loss in function of an organ or extremity is, in the majority of instances, no longer justifiable in the treatment of arterial lesions.

HENRY SWAN.

PULMONARY RESECTION IN THE TREATMENT OF TUBERCULOSIS

THE use of pulmonary resection in some form as a method of treating pulmonary tuberculosis is not a new or recent concept. In 1882 Forlanini prefaced his revolutionary contribution on artificial pneumothorax with a discussion of resectional therapy. He came to the conclusion that resection might be indicated on theoretical grounds, but that it was not then feasible because of the technical limitations imposed by the surgery of his times.

Today these technical limitations have been in large measure dispelled by the enormously

rapid strides made since 1929 in the development of safer procedures for removing all or portions of the human lung. Increases in detailed knowledge of surgical anatomy as it applies to the bronchovascular segments, improvements in anesthesia practice, readily available supplies of blood for supportive transfusion, and the advent of new antibiotics and chemotherapeutic agents have contributed to facilitate safe surgery of the lung. Within a relatively short time these ablational techniques which were developed for the treatment of nontuberculous diseases have been introduced into the therapeutic armament of the phthisiologist. In many clinics today they threaten to displace and even abolish the venerable list of minor and major collapse procedures. We must ask ourselves therefore with some uneasiness and concern whether this trend is correct and whether it is justifiable by the present state of our knowledge and experience.

All but the most reactionary of tuberculosis therapists admit a very large range of indications for resection as opposed to the traditional collapse procedures. Such indications include pathological types of tuberculosis which in past experience have not yielded uniformly and satisfactorily to more conservative measures. Leading this list are the end-results of tuberculosis bronchial disease, bronchostenosis, and bronchiectasis. Also included are the totally destroyed lung, especially when complicated by bronchopleural fistula and tuberculous empyema; for these the proper operation is pleuropneumonectomy. Also to be treated preferably by resection are the cases of circumscribed round focus "tuberculoma" which sometimes are difficult to distinguish from benign or malignant neoplasm.

Another category generally accepted as suitable for resection are those cases in which collapse measures culminating in thoracoplasty have failed to cure the disease, either because cavitational disease, and positive sputum, persist or because the presence of bronchiectasis represented a preoperative complication.

The enthusiastic devotee of the resection method, however, whose experience with resection as a tool is sometimes greater than his knowledge of tuberculosis as a pathological and clinical entity, does not restrict himself to these indications. Resection is proposed, and confidently employed as a method of time-saving, early, and "complete" cure. At one end of the therapeutic scale, resection is proposed for minimal and moderately advanced lesions, types which accumulated experience shows have a better than reasonable prospect of arrest by bed rest and properly chosen minor collapse procedures. At the other end of the scale, resection is being employed for far-advanced and unstable cavitational disease, which actually requires most careful long term medical management with antibiotics before any major surgery is employed, regardless of whether the eventual choice is resection or thoracoplasty.

With acceptance of the basic premise of safe surgical technique and an immediately low operative mortality for resection in its various forms, there still remains the grave and as yet unsettled question of late (or early) complications of surgery, their relative incidence and prognosis. These complications include bronchopleural fistula, tuberculous or mixed empyema, and dissemination of tuberculous disease in the ipsolateral or contralateral lung. It is of more than passing interest that these complications are significantly less when resection is employed for that restricted group of indications generally accepted and stated in the foregoing. The postoperative complications are also decidedly reduced when the patient's disease has had the advantage of long

term stabilization by bed rest, the use of antibiotics and chemotherapy, or previous collapse measures.

The resolution of this interesting conflict between therapeutic procedures will come about when a final evaluation of 5 and 10 year follow-up studies on resection have given us data comparable to what we now have readily at hand for collapse procedures. Patient and physician alike would welcome the establishment of a direct and definitive one stage attack on the various thoracic manifestations of this serious and frequently lethal disease. But rather than jettison the experience and techniques accumulated by our predecessors in a half century's labored progress, it might be well to keep a balanced perspective and to reserve judgment, to employ in the meanwhile all useful available methods as may seem best suited to the case under consideration, and to await the maturation of long term results from our early case experience with resection. Time alone will bring the correct answer.

GUSTAF E. LINDSKOG.

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THE BOOK SHELF

ADOLF

ESTHER H. VINCENT, Evanston, Illinois

ONCE upon a time there was a poor peasant girl who lived in a small town in Austria. Some vagrant passed by one night, and in due course the sorry girl gave birth to a boy, whom she called Alois. The child somehow managed to grow up, and by earnest tugging at his own boot-straps evolved from cobbler's apprentice to customs inspector at a tiny town on the Bavarian frontier. Three times he took unto himself a wife, the last being Klara, some 20 years his junior, daughter of a destitute cottager. It was rumored that Alois and Klara were more or less closely related and that a special dispensation had to be obtained for their marriage. Klara dutifully brought up Alois, Jr., son of her husband's second wife, along with her own Paula, Klara, Adolf, and Angela. At the rather early age of 56 Alois found himself eligible for a pension, and after some restless flitting about, the family at last settled down on a little farm near Leonding, a suburb of Linz.

Alois dreamed of Adolf as a civil service official, but Adolf dreamed of himself as an artist, and the father and son relationship grew strained. Adolf did not do any too well at school, either. In general he took a dim view of education, although he listened eagerly to his history teacher, who was a German enthusiast and an ardent advocate of the Anschluss. Later in life, Adolf liked to picture himself as a boy orator, his playmates hanging breathlessly on his words, but the children thought him a bore, always preaching about something or other. One day, when Adolf was about 14 years old, Alois had a cerebral hemorrhage and died.

Frau Klara, now in her forties, was a simple, modest, kindly woman, tall, with neatly braided brown hair, a long oval face and expressive grey eyes. But she was a weak and doting mother, little able to manage either the tiny farm or the brooding Adolf. So she sold the place and went to Linz, where she rented three rooms in a two-story house across the Danube. It was a clean little flat, with a superb view of the mountains. Alois Jr. had already left to become a waiter in London, and Adolf and his mother and sisters, of necessity, lived very simply and had few friends. They ate cabbage or potato soup, bread or dumplings, drank pear or apple cider, and had meat twice a week. Their clothes were the rough, woolen garments of the poor, the boy wearing the usual Austrian outfit of leather shorts, with embroidered suspenders and feathered green hat. For recreation they took walks in the mountains, listened to free concerts, and read. Adolf buried himself in American Indian stories and reveled in the works of Cooper and Karl May.

At this time he was a quiet, well-mannered youth, tall, slender, and rather sallow, with his mother's fine eyes. In mood he was somewhat melancholy and inclined to introspection. Undoubtedly he was a mother's boy, but the family doctor, Eduard Bloch, thought that the magnitude of affection between them was not at all pathological. Frau Klara let Adolf quit school when he was 16, and he spent the next few years puttering around the house with his paints and brushes. He did not want to work at the post-office and he endured a job as paper-hanger's apprentice for only 6 months.

He was not robust, but neither was he sickly. Dr. Bloch's records make no mention of the pulmonary weakness noted in later stories. The good doctor would treat him for an occasional cold, and when Adolf had tonsillitis, found him obedient and unflinching when he depressed his tongue and swabbed out his throat. On leaving the office, Adolf would courteously bow and thank him.

When Adolf was about 18, he went to Vienna to study art. His mother would have pinched the family budget still more in order to furnish him with a tiny allowance, but Adolf would have none of it, and he signed away his minute inheritance to his sisters. However, he failed to pass the en-

trance examinations at the art academy and on a second attempt was even denied opportunity to take the examinations, so poor was his talent and so meager his schooling. Sad and bitter, he returned home brooding on the unfair discrimination of the academy authorities.

One morning Frau Klara came to Dr. Bloch's office, complaining of chest pain. In a low murmur she told of being kept awake nights, of being too busy to come earlier, of thinking the pain would pass. Examination revealed an extensive mammary cancer, even more serious then than now, for surgical technique was not so advanced. Frau Klara courageously accepted the fact, believing it to be God's will, but Adolf was inconsolable. Tears distorted his long sallow face. Could nothing be done? Dr. Bloch gave but a mere shred of hope.

On an evening in early summer Frau Klara came to the Hospital of the Sisters of Mercy, and was operated upon the next morning by Dr. Karl Urban, the chief surgeon. Thirty years later, this generous, efficient man and his son, a pioneer brain surgeon, were to be forced out of office, and the records of the operation commandeered for the Nazi Party archives in Munich. At Frau Klara's request, Dr. Bloch was present at the operation, and 2 hours later drove to the little flat and told the children. The girls were calm and quiet, but Adolf, his eyes tired and red, his quivering face streaked with tears, asked if his mother suffered. Frau Klara was brought home, but as the weeks and months passed, she could get out of bed for shorter and shorter periods. Adolf slept in the tiny room adjoining hers, and her suffering was mirrored in his face. One December day Dr. Bloch called twice at the house, and the next morning Angela came to his office to tell him that her mother had died quietly during the night.

The doctor had never seen anyone so prostrate with grief as was Adolf, who at last sat down at the bedside and sketched the dead face. They had the funeral on Christmas Eve and buried her beside her husband in the graveyard of the little yellow stucco church at Leonding. A few days later Adolf and his sisters came to the doctor's office to thank him—Paula, fair and stocky, Klara and Angela, pretty, slender and anemic, Adolf, looming up behind, gaunt and pale. He stood there in his black suit with loosely knotted tie, his usual shock of dark hair over his forehead, and finally managed to say, "I shall be grateful to you forever."

Many years later he ordered a Nazi flag to be put on his mother's grave, and when he met Nazis from Linz at a Nuremberg meeting, he asked for news of the town and of Dr. Bloch, the "Edeljude." On his triumphal return to Linz, he visited the grave and showed his gratitude by freeing Dr. Bloch's son-in-law from a 3 weeks' jail sojourn, and by allowing the doctor himself to leave the country with 16 marks instead of the customary 10.

Soon after Frau Klara's death, Adolf left for Vienna to resume his painful growth to manhood. For 3 years he slept in flop-houses, ate free soup, and dreamed on park benches. He earned a little money shoveling snow and carrying luggage, and ambled around vociferously as a hod carrier until the bricklayers threatened to push him off the scaffold. From the speeches of Dr. Karl Lueger, Mayor of Vienna and founder of the Christian Socialist Party, his sulky mind absorbed the poison of malignant resentment.

From his Bohemian flop-house comrade, Reinhold Hanisch, he got the idea of painting postcards of Viennese scenes and heating them before a fire to give them an antique, old master look. Reinhold peddled them about. Some of these cards Adolf sent to Dr. Bloch, who kept them until they were confiscated by the Gestapo. With Adolf's complaint to the police that Reinhold was cheating him, the painting-peddling partnership came to an abrupt end.

Adolf shook the Austrian dust from his shabby shoes and departed to Munich, where he slept on a friend's sofa, worked occasionally, and frequented meetings where he discovered his talent for political histrionics. At the beginning of the first World War he barely escaped arrest as an Austrian deserter by enlisting in the German Army. Here he stayed at the level of private, first class, and it is unlikely that his Iron Cross was officially bestowed. Reports of his wounds and mustard gas blindness are also disputed. His company was gassed, but Adolf recovered his sight in a few days, and his "blindness" was probably hysterical. A story went the rounds that he was cured after a vision of the Virgin who promised him recovery if he would never aspire to the officer class. Adolf's captain is reported to have said, "I shall never make this hysteric an N. C. O.!"

At the close of the war, fearful of losing his regular meal ticket, Adolf remained in the army, idling away his time in barracks for 2 years, when the post was disbanded and he was sent to Munich, still on the army payroll. Here he became "teacher's pet" in Ernst Röhm's classes where men were being trained to become demagogues or secret observers. Assigned to attend the beer-cellar meetings of the German Workers' Party, Adolf gradually developed it into the Nazi

Party, ranting away in hired halls, where his remarkable gift of transmitting emotion roused his beaten, resentful audiences to frenzy. Eventually his bid for power brought on a charge of high treason and he spent the next 5 years as a distinguished prisoner in a fortress. Here it was that his growing emotionalism produced tears at the slightest frustration, and here also his belief in his Messianic mission became the focal point in the extraordinary power of his personality.

During his struggle for power he would at times fall into fits of melancholy and make threats of suicide without meaning them, but when he became Chancellor his self-pity was covered by waves of self-adoration, and he would find voluptuous pleasure in making speeches with the whole of Germany as audience. He still lived rather simply, did not drink or smoke, and was careful as to his health. Like many Upper Austrians he had always preferred meat to sweets, but now he gave up meat entirely. Exhilarated by his growing sense of dynamic energy, he would rise up from his modest supper of vegetable pie and distilled water, and prance upon the table, identifying himself, not with Napoleon or the Caesars, but with Attila or Genghis Khan.

Like all dictators Adolf lived in constant fear of assassination, and so was not completely surprised by the abortive attempt to kill him at Rastenburg. The plot, long smoldering underground, broke out when defeat at last shattered the myth of his military omnipotence. The bomb, concealed in a brief case, was laid against a table leg in the conference room. How Adolf escaped is still not clear. Perhaps he moved away or the peculiar construction of the table protected him. As it was his eardrums were pierced, his right arm bruised, his uniform torn, and he fell dazed into the arms of a companion. While four men lay dead or dying about him, he lived. Had the conference taken place in the usual concrete bunker, instead of in a wooden hut, none would have survived. That same day, white as a sheet, he went to meet Mussolini and to talk over the affair at a Mad Hatter's Tea party.

Meanwhile the first doctor to be summoned was Erwin Giesing, otologist at a nearby military hospital. Later came Von Eicken, the Berlin specialist, who found that the tympanic membranes of nearly all the officers present had been broken, Adolf's on both sides. The labyrinthine irritation produced disorders of balance, and there was a subcutaneous hemorrhage of the right arm. Adolf was sent to bed and recovered in a month. But he withdrew from public life so completely that many believed him dead or imprisoned.

Before the War, Adolf lived his usual irregular, bourgeois existence in Munich, planning, conferring, making tours of inspection, going to picnics or picture shows, and spending long week-ends at Obersalzberg. He is said to have delighted in the companionship of his buxom blonde niece, Geli, whose mother became his housekeeper. But he lost Geli when she went to Vienna to become a dancer and died from a bullet wound.

During the War he was the great war lord, working hard and long, with no relaxations, no safety valves. Awakened about noon, he spent hours interviewing politicians and generals, adjutants and liaison officers, doctors and secretaries, stopping at odd moments to eat, to stroll in the garden, or to take an evening nap. Sometime between two and three o'clock in the morning his day would end with a nonpolitical tea party and then bed. Toward the last he limited his sleeping hours to three.

Dr. Von Hasselbach, the most critical and reliable of his physicians, and one of the few "courtiers" immune to his personal magnetism, reports that up to 1940, Adolf looked young for his age, but then aged so rapidly that he soon became senile. This sudden deterioration was due to his abnormal way of life and to bad medical advice. To endure association with his undisciplined personality, Adolf's constitution must have been extraordinarily strong to begin with. Before the War his only complaint was a throat affection, diagnosed by Von Eicken as a polyp on the vocal cords. This was removed with complete voice recovery, and, except for stomach cramps and an occasional tingling in the ears of hysteric origin, Adolf was well enough until 1943. However, he thought he had heart trouble, and after 1938 avoided all exercise, and even refused to ascend by elevator to his expensive observation post above Berchtesgaden, because of the altitude (5,400 feet). He said it made his chest feel tight. But his doctors could find no sign of an organic cause for this or for his epigastric pain.

Adolf had three principal physicians—Brandt, Von Hasselbach, and Morrell. Brandt and Von Hasselbach may not have been the most skillful of physicians, but at least they were professionally reputable. Morrell was a quack, a gross but deflated old man, cringing in manner, inarticulate in speech, and slovenly in dress and habits. But Adolf kept him in constant attendance for 9 years. Morrell always maintained that he was the true discoverer of penicillin, the secret of which had been stolen from him by the British. He had set himself up as a specialist in venereal diseases in Berlin and came to Berchtesgaden as an attendant

on Adolf's photographer. He manufactured his own medicines in priority built factories and their purchase was made compulsory throughout the Reich. The armed forces were commanded to use his "Russia" lice powder. From his own account, Morrell used 28 different drug mixtures on Adolf, including various fake drugs, narcotics, stimulants, and "ultraseptyl," a sulfonamide produced by his Budapest factory and condemned by the Leipzig Pharmacological Faculty as a nerve poison. His favorite method of administration was injection, and he would give massive "shots" of sulfonamides for slight colds. Adolf felt better after a big dose of dextrose, hormones, vitamins, etc., and whenever he thought he was going to have a cold, he would have 3 to 6 injections daily with some therapeutic success, but as a prophylactic this treatment broke down his normal resistance. During the entire War, Adolf and most of his staff were getting almost continual "shots."

Although Morrell managed to cover up exhaustion by artificial stimulants, the first symptoms of Adolf's physical change were apparent by 1943. His left arm and leg trembled, his left foot dragged, and he developed a stoop. Following the shock of the 1944 bomb blast, the tremors ceased for a time only to reappear in aggravated form. He continued his eccentric mode of life in the damp bunker in East Prussia, shunning all fresh air, fearing exercise, and suspecting danger everywhere. His once loud, ranting voice grew weak and faint. Von Eicken removed another polyp from his vocal cords and treated him for maxillary sinus infection and for swollen neck glands. Except for a daily staff conference, Adolf stayed in bed for 6 weeks, attended by a parade of physicians—Von Eicken, Morrell, Weber (heart), Blaschke (teeth), and others. In September came the Great Medical Battle in direct consequence of the Morrell treatment. When Adolf's stomach cramps were at their worst, Dr. Giesing found out that for at least 2 years Morrell had been giving Adolf a proprietary drug known as Dr. Koester's antigas pills, a compound of strychnine and belladonna, which, administered in doses of 2 to 4 pills with each meal, was causing a progressive discoloration of the skin. Giesing informed Brandt and Von Hasselbach, who ventured to suggest to Adolf that these pills might be poisoning him. But Adolf would not believe it and dismissed them both. Later he had Brandt arrested and condemned to death, from which he was saved by the deliberate procrastination of friendly officials.

Morrell was now in complete charge except for the occasional presence of Karl Gebhardt, Himmler's surgeon and evil genius, the man who had made experimental operations on Polish girls at Auschwitz, and who had become President of the German Red Cross. And then there was Ludwig Stumpfegger, a really competent orthopedic surgeon, who was unaccountably bewitched by Adolf. A faithful giant, Stumpfegger bowed in adoration before his god and remained with him to the end.

Adolf was now reduced to a trembling specter, with emaciated face, grey skin, stooping body, shaking hands and feet, and quavering voice. The film of exhaustion covered his hypnotic grey eyes, the magnetism of which never showed up in photographs. Full of suspicion, given to fits of blind rage, alternating between insane optimism and black despair, he yet gloried in the thought of the blazing funeral pyre of Nazi Germany. Though physically afraid of blood, he yet lusted after the thought of it.

Fifty feet beneath the vast marble ruin that was once the Berlin Chancellory, Adolf and his still sizable court cowered in the two-level bunker. With him was Eva Braun, whose schoolgirl mentality had furnished him secret companionship for 12 melodramatic years. Eva was no Pompadour and it is probable that their last minute marriage was merely symbolic. One day the poison was passed around, the dogs were killed, the petrol got in, and the guns loaded. Early in the afternoon Adolf and Eva went into their sitting room. Presently a single shot was heard and Adolf was found, shot through the mouth, lying on a blood-soaked sofa. Eva also lay back on the sofa, poisoned. At half-past three came the Viking funeral. Adolf's body was wrapped in a blanket to conceal the shattered head, but his legs in the familiar black trousers stuck out. There was no need to cover Eva. As the procession moved out of the emergency exit into the garden, it collided with a guard who fled. The bodies were placed side by side, drenched with petrol and fired. The sheet of flame was accidently seen by another guard on the wall, and a third guard was driven away by the stench of burning flesh. As the flames died down more petrol was thrown on by the S. S. men. Three men had been chosen to bury the remains, for, although 180 liters of petrol burning slowly on a sandy bed would char flesh and dry up fluids, there would be left some fragile human remnants. The bones were never identified and may have been broken up and mixed with others, for, when the Russians arrived, nosing around through the cold, dead smell of fire, they dug up many bodies. And the men who left Adolf's engagement diary unobserved in his chair for 5 months may have missed seeing other things carefully hidden.

Many psychiatrists tried to diagnose the case of Adolf at long distance. He was called a paranoic, an epileptic, an Oedipus complex victim, and a hysteric. It is true that hysterics have seldom been found among politicians and rulers, but one remembers Tiberius, Claudius, and Caligula. All he had was his late-found power of spellbinding, but his essentially negative personality was fired to hypnotic levels by early frustrations and by subconscious desires to be revenged on a society that had produced but did not want him. On a proud, easily deluded people, smarting under a sense of undeserved defeat, the impact of Adolf was fatal.

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REVIEWS OF NEW BOOKS

THE surgeon who has casually thought of plastic surgery of the nose as comprised of the removal of unsightly humps and in correcting the deformity of a saddle nose with a cartilage transplant will gain new insight both into the complexities and the possibilities of such surgery by a careful reading of Brown and McDowell's excellent monograph, *Plastic Surgery of the Nose.*[1]

This volume includes in a full measure the four elements essential for completeness in a work of this kind: careful anatomical descriptions of the normal and of the abnormal; concise and accurate descriptions of the recommended surgical technique; illustrations that help to make the descriptions pointed and clear; and finally numerous and adequate photographic reproductions of the preoperative condition and the postoperative results. For the many and clearly depicted anatomical sketches and diagrams of surgical procedures Miss Gertrude Hance deserves great credit, and her contribution to the excellence of this volume is not a small one.

Approximately the first half of this monograph is devoted to a discussion of general considerations—the correction of the deformities resulting from excessive size of the nose, indications for operation, anatomical considerations, preoperative study and preparation of the patient (section 1) and to reduction in the size of the nose (section 2). Section 3 is devoted to building up and straightening the nose, and in this section and the remaining portion of the volume is included the surgical treatment of the many deformities and conditions resulting from injury, both old and recent, deformities following operation for cleft lip, those following luetic disease, excessive radiation, and deformities resulting from benign and malignant growths and from the treatment of such growths.

Chapters on composite free grafts of skin and cartilage from the ear to the nose, and on war injuries of the nose, depict exceedingly well the excellent results obtained in the treatment of the serious and extensive injuries resulting from war wounds and burns.

It is impossible in a limited review to enter into a discussion either of the general plan or of the details of operative procedures, but rarely has this reviewer seen such concise, clear-cut and comprehensive descriptions and diagrams of operative procedures—descriptions that leave no doubt in the mind of the reader as to the exact method of the authors' attack on the problem at hand.

No one can even glance cursorily through this volume without being aware of how large a contribution to happiness and better living the conscientious and skillful plastic surgeon can make. Among the men who are doing such work the authors of this volume stand very high. SUMNER L. KOCH.

[1]PLASTIC SURGERY OF THE NOSE; INCLUDING RECONSTRUCTION OF WAR INJURIES AND OF DEFORMITIES FROM NEOPLASTIC, TRAUMATIC, RADIATION, CONGENITAL, AND OTHER CAUSES. By James Barrett Brown, M.D., and Frank McDowell, M.D. St. Louis: The C. V. Mosby Co., 1951.

THE new work on *Electroencephalography in Clinical Practice*[2] was written primarily to discuss the uses and limitations of electroencephalography in the diagnosis and study of diseases of the nervous system. As stated in the preface, the book is intended for neurologists, internists, psychiatrists, and neurosurgeons. It is not a manual for the electroencephalographer, nor in any sense a textbook in this field. It represents essentially the personal experiences and viewpoint of a neurologist who has been active in clinical electroencephalography for 12 years. Electroencephalography achieves its best results when it is combined and correlated with the usual diagnostic procedures of the neurologist, psychiatrist, and neurosurgeon. For the neurologist this procedure should stimulate curiosity about the relationship of known areas of pathology to the function of the brain itself. The examination should be of value to the neurosurgeon in encouraging operative intervention in some patients or withholding it in others.

The first 2 chapters deal with the history and the relation of electrophysiology and anatomy of the brain to electroencephalography.

The third and fourth chapters deal with the normal and abnormal electroencephalogram and a discussion of the technical aspects of performing the test. Formerly, it was necessary to enclose the subject in a grounded, screened room called a faradic cage. The newer equipment is so well balanced and shielded in its cabinet that shielding is not required to obtain satisfactory records.

A full chapter is devoted to epilepsy. The value of electroencephalography in this condition cannot be overemphasized. The diagnosis can be established in ordinary recording in 85 per cent and with activation techniques in 95 to 100 per cent of cases. The value of the electroencephalogram is also clear in the differential diagnosis of convulsive seizures.

The chapter on neurological and neurosurgical problems is stimulating and instructive.

The electroencephalogram can tell us if the record is normal or abnormal, if the abnormality is localized, lateralized, diffuse, deep, paroxysmal, or continuous. Trauma to the brain produces electroencephalogram findings. As recovery takes place, there is usually a steady improvement demonstrated in the electroencephalogram.

As regards tumor diagnosis and localization, four questions may be asked: (1) How often does it localize

[2]ELECTROENCEPHALOGRAPHY IN CLINICAL PRACTICE. By Robert S. Schwab, M.D. Philadelphia, London: W. B. Saunders Co., 1951.

when other methods fail? In 5 per cent of cases. (2) How often does it confirm the localization of other techniques? In 80 per cent of cases. (3) How often does it aid in eliminating the possibility of neoplasm when the tracing is normal? In 90 per cent of cases. (4) How often does it mislead in 1, 2, or 3? In 5 per cent of cases.

The last 3 chapters deal with electroencephalography in psychiatry in research; and a full chapter is devoted to laboratory organization, training of staff, and interpretation of records.

This volume is highly recommended to all of those interested in neurology, psychiatry, and neurosurgery. The book contains excellent illustrations and tracings and is written in a pleasing style. It represents a worthwhile addition to other books and manuals on the subject of electroencephalography.

HOWARD H. LANDER.

THE 1951 volume of *Monographs on Surgery*[1] is a worthy companion of the excellent 1950 volume and includes a number of comprehensive studies on subjects of particular interest to the specialist in gynecology, urology, and orthopedics as well as to the general surgeon.

The first series of papers, preceded by a brief introduction by Joe V. Meigs, is devoted to the subject of carcinoma in situ of the cervix, and five excellent papers by Richard W. Te Linde, Paul A. Younge, Howard Ulfelder, Edgar R. Pund in association with Joe M. Blumberg, and Ruth M. Graham present the present day concept of the diagnostic problems involved and the treatment of this very early type of carcinoma of the cervix.

In his introduction of the subject, which includes a helpful glossary of a number of terms frequently not understood or misunderstood, Meigs makes a comment which deserves repeating, "A glossary is appended in an attempt to interpret the various nomenclatures and to group them and make for better understanding. For the sake of the patient and her doctor, simplicity, even though the terminology offends certain investigators, is more important than the investigators' sensitivity to names. Simplicity in medical writing is important, and avoidance of the more unusual terms found in the histologies and pathologies, in the medical dictionaries, and in the thesaurus is paramount. Word confusion is destructive to understanding."

Concerning the diagnosis of carcinoma in situ there is rather general agreement among the authors of these five papers, and the importance of the Schiller test and of cytological diagnosis by Papanicolaou's method is repeatedly emphasized. Concerning treatment there is divergence of opinion since it has been shown that in some cases regression of the disease occurs and that in a definite number of cases cure has followed cauterization of the cervix.

[1]MONOGRAPHS ON SURGERY 1951. Edited by B. Nolan Carter, M.D., Ph.D., New York, Toronto, Edinburgh: Thomas Nelson & Sons, 1950.

Te Linde says, "In 1939 Galvin and Te Linde undertook a histologic study on cervices that had been removed following a biopsy diagnosis of carcinoma in situ. The patients were treated by total hysterectomy so that the entire uterus was available for study. The removed cervices were cut up completely in blocks and many sections made of each block in a search for microscopic invasive cancer. In a total of 108 cases, microscopic invasive cancer was found 72 times. It is only fair to say that there is often some difference of opinion as to what constitutes invasion.

"A total of 99 women has been treated surgically during the decade and 9 by irradiation.... The only death occurring in the entire series of 108 was in a patient who had been treated by irradiation.... All of the 99 women on whom hysterectomy was performed are living and well.... Our results with surgery have been so satisfactory that we see no reason for changing our line of therapeutic attack on this problem."

Younge expresses a somewhat different viewpoint. "*This patient* (well 13½ years after removal of a section for biopsy and subsequent cauterization) *and 22 others all showing definite carcinoma in situ have been followed from three to 14 years and apparently have been cured, in most cases unwittingly, by cauterization of the cervix.* Six others were cured also as demonstrated by negative serial block study of the excised cervix one month to six years later.

"Fourteen patients who for the most part have had carcinoma in situ with glandular involvement were not cured by cauterization of the cervix, but the delay in treatment did not jeopardize the eventual outcome because all have been cured by subsequent hysterectomy one to 14 months after the original biopsy. There has been no recurrence of the disease following more radical treatment in (any) one of these patients although a hysterectomy was not performed in some cases up to 14 months after the disease was first recognized."

Ulfelder says, "Removal of the uterus has been almost standard therapy here."

Pund and Blumberg state, "If a cytologic film from the cervix is found to contain cells strongly suggestive of cancer, in other words, a positive Papanicolaou test, we recommend multiple biopsies and endocervical curettage. When this surgical procedure is carried out in the operating room, we further recommend that a cautery conization of the cervix be done at the same time. If study of the biopsy and endocervical curettage gives evidence that the carcinoma is in its preinvasive stage, it is recommended that this patient be followed by cytologic studies to determine if the carcinoma has been eradicated. If a subsequent film proves positive, total hysterectomy is indicated. If invasion is found, the depth and extent of the invasion are determined in so far as possible by the examination of multiple biopsies and endocervical curettage. When invasion appears superficial, an exploration is recommended with hysterectomy as a goal.

"We do not now believe that it is necessary to remove the uterus in all cases. We do believe an attempt at eradication of the cancer should be made by cauterization in the younger age group."

Dr. Graham comments, "... it would seem that about 40 per cent of the patients with preinvasive carcinoma go on to develop a truly invasive tumor. But what of the other 60 per cent who are free of disease even though the treatment was poor by present standards? ... Younge, Diddle, Pund, and their co-workers have described lesions which histologically are identical with carcinoma in situ occurring in pregnancy and disappearing post partum. Can we assume that in every instance the entire tumor was removed by these minor procedures? It appears to us that the answer to these questions is that the tumor may in some instances be reversible.... If these tumors are reversible, it is of great importance. It would mean that perhaps there is a stage where the tumor may progress in either direction.... It is well known that when a tumor becomes invasive it only progresses toward more invasion if untreated. But can we be sure that we may apply that same rule to these early lesions? ...

"The study of these cases is of first importance and if all are operated on without extensive study, we as a group have neglected a real opportunity to increase the knowledge of beginning cancer."

Altogether, this group of papers indicates again how much thought and study are being given to this important problem.

Appropriately an excellent chapter on the cytologic diagnosis of cancer by Peter A. Herbut and Abraham E. Rakoff is included in this volume. The major emphasis is on diagnosis of cancer of the female genital tract, cancer of the lung, the prostate and urinary tract. A discussion of technique and excellent illustrations, some in color, add to the completeness of the presentation.

For the specialist in urology, in addition to the chapter just mentioned are two chapters: one on diagnosis and treatment of the infertile male by Fred A. Simmons and a second, the surgical management of prostatic disease by Stanley H. Moulton and Charles Huggins.

Dr. Simmons' 40 page chapter is an exhaustive discussion of the problem of infertility and offers a comprehensive plan of meeting the problem. Its importance may be judged by his statement, "It is estimated that there were, a decade ago, 3,500,000 involuntary sterile marriages in the United States, and of these 2,100,000 husbands may be presumed to be infertile."

The author stresses the importance of an adequate history, a searching physical examination, of repeated examinations of semen obtained in a definitely prescribed manner and examined under suitable conditions. The indications for testicular biopsy and the technique are carefully described, but the outstanding impression gained by the reader is the author's constant insistence on attention to the many factors that are involved in "right living."

Stanley H. Moulton's and Charles Huggins' chapter on the surgical management of prostatic disease is a clear cut and concise résumé of the indications and contraindications for transurethral resection, perineal, suprapubic and retropubic prostatectomy. The advantages and disadvantages of each method are stated, and the methods used and results obtained in 300 recent consecutive prostatectomies at the University of Chicago Clinics are tabulated. This discussion of retropubic prostatectomy closes with the statement, "In this country the original enthusiasm for the retropubic approach is waning. It is now recognized that the approach is technically difficult and that the complication of osteitis pubis is appreciable.... At the University of Chicago Clinics the retropubic approach has been abandoned."

Carcinoma of the prostate presents a difficult and disheartening problem. "Necropsy studies have shown that 18 per cent of men over 50 have carcinoma of the prostate." Since diagnosis in the early stage is difficult and since the only cure is radical operation before the disease has extended beyond the prostatic capsule the results of treatment are discouraging. Orchiectomy and estrogen therapy do offer hope for improvement and relief of symptoms which may persist for considerable periods. "Some 90 per cent of patients treated with antiandrogenic therapy show a distinct and immediate improvement. Within two years, 55 per cent of these are followed by relapse and within five years, 75 per cent are dead. About 20 per cent live more than eight to 10 years."

Both the specialist in orthopedic surgery and the general surgeon will find grist for his mill in three excellent papers on Some Congenital and Developmental Problems of the Hip Joint in Infancy and Childhood by Frank P. Kreuz and Alfred R. Shands, Jr., on Bone Tumors and Their Treatment by Murray M. Copeland and Charles F. Geschickter, on Internal Derangements of the Knee by Edwin F. Cave, and in four papers of especial interest to the general surgeon: Cholangiography by Philip F. Partington and Maurice D. Sachs, Regional Enteritis by Leland S. McKittrick and Thomas S. Risley, Ulcerative Colitis by the same authors and Diaphragmatic Hernia by Stuart W. Harrington.

It is a matter of regret that space does not permit more extended comment on these contributions. Each is written by men of wide experience in the particular field under survey, all are exceedingly well illustrated, and fulfill the objective of presenting a well rounded, comprehensive and critical appraisal of difficult problems of real importance in present day surgery. SUMNER L. KOCH.

THE 720 page *Text-Book of X-ray Diagnosis*[1], volume 2, deals with diseases of the chest including both the cardiovascular and respiratory

[1] A TEXT-BOOK OF X-RAY DIAGNOSIS. By British Authors in 4 Volumes. Vol. 2, 2d ed. Edited by S. Cochrane Shanks and Peter Kerley. Philadelphia & London: W. B. Saunders Co., 1951.

systems. The production of the second edition of this excellent work covering the entire field of roentgen diagnosis with the addition of new material necessitated an increase in size and the textbook has been rearranged in 4 volumes subdivided into the head and neck, the chest, the abdomen, and the bones and joints. Such a division should prove convenient to clinicians interested in a special branch of medicine. The list of contributors includes 17 recognized British authorities. Not only is the field of radiology represented but contributions are included from the surgeon, pathologist, and internist.

As in previously published volumes, the subject matter of volume 2 is presented in a clear, concise, and logical manner, and whenever indicated included are pertinent clinical and pathological discussions. The text is divided into two parts, the cardiovascular system contributed by Dr. Peter Kerley and the respiratory system by the late Dr. E. W. Trining, revised by Dr. Peter Kerley. Newer developments in the diagnosis of intrathoracic diseases are adequately and completely covered. The volume is well illustrated with 605 excellent reproductions of well chosen roentgenograms, pathological material, and line drawings with adequate captions.

The British authors and the publisher have done a splendid job. The reviewer is using these excellent volumes extensively in his daily work and in teaching. He welcomes the opportunity to recommend this second edition not only to radiologists and postgraduate students of radiology but to specialists in the branch of medicine covered by a specific volume, with volume 2 recommended particularly to the internist, cardiologist, thoracic surgeon, and physicians interested in diseases of the chest.

EARL E. BARTH.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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